

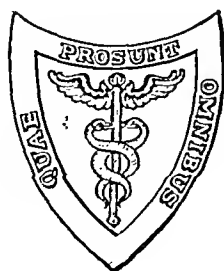
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THE
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JULY, 1936

ORIGINAL ARTICLES.

ON THE EXISTENCE OF AN INTRINSIC DEFICIENCY IN
PELLAGRA.

A PRELIMINARY REPORT.

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FOR a number of years there has been doubt of the total validity of Goldberger's theory that pellagra is entirely a manifestation of nutritional deficiency. McLester¹ has pointed out some of the objections to this hypothesis. It has been the experience of many that severe advanced cases are poorly controlled by diet and vitamin therapy. Of 440 cases of pellagra observed in this clinic during the 15-year period, 1919 to 1934, 119 (27.02%) died. The mortality rate, during the years 1924 to 1934, when yeast was used lavishly to fortify the diet, was 25.5% which compared favorably with the rate of 37.5% which prevailed before that time, but was still discouragingly high. Several observers, including Spies^{2,3} and the authors, have seen remission or recovery while patients were on pellagra-producing diets. It is well known that chronic alcoholism and extensive neoplastic or obstructive lesions of the stomach may

be associated with the development of pellagra. Occasionally the disease has been seen to occur in individuals seemingly adequately nourished in all respects and free from alcoholism or obstructive disease of the gastro-intestinal tube. Since the discovery of the relation of liver extracts and desiccated stomach to recovery in pernicious anemia, Spies,^{4,6,7} Ruffin and Smith,⁵ and others have drawn analogies between this disease and pellagra and have had success in treating pellagra with liver and stomach preparations. Improvement in patients so treated has been attributed to a protective influence exercised by stomach on vitamin B₂ or to the high B₂ content of liver extracts, but Spies³ suggested a secondary factor analogous to the gastric deficiency in pernicious anemia.

Pellagrins clinically may be separated into three general groups: The mild, who recover spontaneously on diets nutritionally inadequate but fairly high in calories; the severe, who mend slowly on a diet high in calorie value enriched with vitamins; and the intractable, who are prone to die febrile or demented in spite of all remedial measures. Admitting that an extrinsic deficiency is active in the production of pellagra and that the essential substance is in all likelihood the B₂ complex; and not denying that factors as diverse as infection, seasonal influences and excessive solar radiation may play a part in the genesis of the disease, an explanation is necessary for the fact that many patients fail to improve when the essential substance is administered even in great excess. If it could be shown that an intrinsic factor exists which is necessary for the utilization of the extrinsic factor B₂, many of the paradoxes of pellagra might be explained. It might be inferred that prolonged deficient intake of extrinsic factor leads to exhaustion or failure of production of intrinsic factor in certain individuals with development of the syndrome complex of pellagra. In some, sufficient intrinsic factor may remain or be regenerated to make possible utilization of minimal amounts of extrinsic factor. In others, a large intake of extrinsic factor may promote rapid regeneration of intrinsic. In others still, intrinsic factor is lacking and cannot regenerate even in the presence of abundant extrinsic factor which, therefore, is not utilized.

In imitation of the work of Castle and his associates⁸⁻¹² on pernicious anemia it was determined to test the efficacy of normal gastric juice as a source of an hypothetical intrinsic factor. The patients to whom gastric juice was given were typical advanced cases of pellagra. Recent alcoholism and obstructive lesions of the gastro-intestinal tract were absent.

Method. Five patients were maintained on the original Goldberger-Wheeler : " : diet to which was added 25 gm. of fat salt pork. As : : : : : had a daily caloric value approximating 1400 C. and contained approximately 260 gm. of carbohydrate, 25 gm. of protein

and 30 gm. of fat. Sources of B₂ were minimal, collards being the only article of diet containing it in appreciable quantities. One patient was desperately ill and stuporous and was given the routine liquid pellagra diet used in treatment of the most severe cases. In the absence of any quantitative method of estimating improvement or regression impressions were based on the mental state, progress or resolution of dermatitis, glossitis and stomatitis, frequency of stools and gain in weight. Three patients were held on the pellagra-producing diet for a preliminary observation period of 2 weeks or more. One patient was given during the observation period amounts of hydrochloric acid comparable to the normal daily secretion. As items of interest weekly analyses of gastric juice obtained after histamin were recorded and tongue prints were made at weekly intervals. It is not to be inferred that any relation is implied between the degree of gastric acidity and the presence of intrinsic factor. Gastric juice was obtained from normal medical students and from patients with no gastrointestinal disease. To obviate the probability of increased gastric digestion of food, all doses of gastric juice were administered in the evening some 4 hours after the evening meal.

Case Abstracts. CASE 1. (No. 92931.) B. R., female negro, aged 45, was admitted, October 25, 1934, with symptoms of 4 months' duration. She was emaciated, weighed 75 pounds and had a typical pellagrous dermatitis of forehead, face, hands, forearms and feet. The tongue was bright red with advanced papillary atrophy; there was moderate stomatitis. Diarrhea with 4 to 5 stools daily had been present for 1 month. Temperature, 99° F.; pulse, 110; respiration, 24; blood pressure, 96/74. General physical examination was not remarkable. The urine was negative. The blood contained hemoglobin, 80%; R.B.C., 3,930,000; W.B.C., 8300. Routine blood chemical determinations were normal. The Wassermann and Kahn tests were positive. Analyses of gastric contents are tabulated below.

TABLE 1.—ANALYSES OF GASTRIC CONTENTS.

Date.	Free HCl.	Total acidity.
1934.		
Oct. 25	0	5
Nov. 17	0	8
29	0	8
Dec. 6	44	60
12	39	54
24	20	42
31	15	35
1935.		
Jan. 26	40	58

This patient was fed the regular ward diet for 22 days, during which she became slightly worse, with increasing stomatitis and diarrhea. Her weight on November 17 was 75½ pounds, when she was put on pellagra-producing diet. During the ensuing 2 weeks there was definite increase in dermatitis and stomatitis, diarrhea, with 5 or 6 stools daily, persisted. On November 29, her weight was 75½ pounds. On this day and the 9 ensuing days she was given 200 gm. of ground raw lean beef incubated with 200 cc. of normal gastric juice, according to Castle's technique,¹⁰ which was administered at 8 P.M. by stomach tube. On December 2, marked improvement in the stomatitis and glossitis was noted. On December 6, stomatitis was healed, the tongue had lost its glossy redness, there was beginning desquamation of the skin lesions, and diarrhea had lessened to 2 stools daily. Subjective improvement was marked and the weight was 78 pounds. On December 9, after 10 doses of beef incubated in gastric juice, treatment was discontinued. Clinical improvement was remarkable,

the mouth looked normal, the tongue was pink and showed regeneration of papillae. The skin lesions were far advanced in resolution and stools reduced to 1 daily. It was decided to maintain this patient on pellagra-producing diet and to expose her to direct sunlight in an effort to produce a relapse. She continued to show clinical improvement with complete resolution of skin lesions, absence of diarrhea and subjective well-being. On December 24, the weight was 83 pounds; on January 6, 1935, she was dismissed, clinically cured, weighing 88 pounds. She was observed on January 26, when gastric contents were secured, and at intervals until September 1, 1935. There has been no recurrence of pellagra.

COMMENT. This patient, after administration of 200 gm. of raw beef incubated with 200 cc. of normal gastric juice daily for 10 days, showed extraordinary improvement which was maintained during a subsequent observation period of 4 weeks, during which she remained on pellagra-producing diet and was frequently exposed to sunlight. Eight months later no signs of pellagra could be detected. It is felt that this woman cannot be said to have improved as a result of gastric juice alone; the lean beef used is considered an excellent source of B₂. The rather spectacular remission may have been due to administration of large amounts of both extrinsic and intrinsic factor. On this account no similar experiment was carried out.

CASE 2.—(No. 93433.) H. S., aged 33; a white male, was admitted, November 11, 1934, with symptoms of 4 months' duration. He was fairly well nourished; weighed 131 pounds. Typical pellagrous dermatitis of malar eminences, hands, forearms and feet. The tongue was smooth, bright red and fissured; there was no marked stomatitis. Diarrhea had been present for 6 weeks, averaging 5 stools daily. Mild dementia was present. Temperature, 100° F.; pulse, 88; respiration, 20. General physical examination showed nothing unusual. The urine was negative. The stools contained no parasites. The blood contained hemoglobin, 80%; R.B.C., 4,580,000; W.B.C., 6700. The Wassermann and Kahn tests were positive. Routine blood chemical determinations were normal. The results of analyses of gastric contents are tabulated below.

TABLE 2.—ANALYSES OF GASTRIC CONTENTS.

Date.	Free HCl.	Total acidity.
1934.		
Nov. 12	0	8
25	0	7
Dec. 1	0	14
8	32	43

This man was put on pellagra-producing diet for 2 weeks, at the end of which dermatitis and glossitis were worse; diarrhea was somewhat less, averaging 4 stools daily. The mental state was distinctly worse; he was morose, irritable and inclined to be uncoöperative. From November 25 to December 4, inclusive, normal gastric juice in amounts varying from 150 to 300 cc. was given daily at 8 p.m. On December 1, definite improvement could be noted; the tongue was pink and showed slight regeneration of papillae; the skin lesions were beginning to leave smooth red surfaces. The stools were reduced to 2. The diet was continued until his dismissal from the hospital, on December 13. At this time he was clinically well. The tongue looked normal, the areas of dermatitis had

completely desquamated, stools were 1 daily and the mental state seemed normal. The weight was 133 pounds.

CASE 3.—(No. 93485.) R. M., a white female, aged 58, was admitted, November 21, 1934, with symptoms of 3 weeks' duration and sudden onset, on November 1, with diarrhea and soreness of the mouth and tongue. Eruption appeared on the hands about November 15. She had been under observation and treatment in the Out-Patient Department since November 5. She was fairly well nourished; weight, 128 pounds. There was edema and bright red erythema of the forehead, bridge of the nose, hands, wrists and forearms. The tongue was bright red, ulcerated at the edges, slightly atrophic; there was moderate stomatitis. General physical examination revealed nothing significant. The temperature was 100° F.; pulse, 88; respiration, 20. The urine contained traces of albumin. The stools contained no parasites. The blood contained hemoglobin, 70%; R.B.C., 3,600,000; W.B.C., 8750. Routine blood chemical determinations were normal. The Wassermann and Kahn tests were negative. Results of analyses of gastric contents are tabulated below.

TABLE 3.—ANALYSES OF GASTRIC CONTENTS.

Date.	Free HCl.	Total acidity.
1934.		
Nov. 22	0	7
28	28	36
Dec. 5	20	22
12	12	27
1935.		
Oct. 3	5	17

Since this woman was acutely ill with slight fever, a rapidly developing eruption and severe diarrhea averaging 9 stools daily, it was not thought wise or necessary to hold her for an observation period. She was given the pellagra-producing diet, and normal gastric juice in amounts varying from 160 to 270 cc. were given daily from November 22 to December 1, inclusive. On November 24, definite recession of dermatitis and stomatitis was noted and the stools were reduced from 9 to 3 in 24 hours. On December 1, dermatitis had resolved, leaving slight reddening of the skin, and stomatitis and glossitis had disappeared. Stools were 1 daily. She was subjectively well. She was kept on pellagra-producing diet during the remainder of her stay in the hospital and discharged, December 13, clinically well. She has been followed up to the present time and has had no relapse.

CASE 4.—(No. 93928.) J. H., a negress, aged 23, was admitted, December 13, 1934. There had been 3 previous admissions to the hospital, on March 16, 1931, July 9, 1931 and May 4, 1932. On each occasion the diagnoses were pellagra and sickle-mia. The present relapse began 4 weeks before admission, with diarrhea up to 6 stools daily; stomatitis and dermatitis appeared 3 weeks before admission. She was emaciated; weight, 71½ pounds. The forehead, nose, cheeks and chin presented the "pellagrous mask." There was severe moist dermatitis of the hands, wrists and forearms, dry dermatitis of elbows, feet and ankles. There was vaginitis thought to be of pellagrous origin. There was severe stomatitis, the tongue was atrophic but not red or ulcerated. There was slight mental confusion. General physical examination showed no other gross abnormalities. The temperature was 99° F.; pulse, 92; respiration, 20. The urine was concentrated and contained a few leukocytes. The stools contained no parasites. The blood contained hemoglobin, 30%; R.B.C., 1,650,000; W.B.C., 9000. Sickle-mia was present. Routine blood chemical determinations were normal. The Wassermann and Kahn tests were negative. Results of analyses of gastric contents are tabulated below.

This patient was put on pellagra-producing diet with no preliminary observation period. It was decided to give hydrochloric acid in amounts theoretically equivalent to normal daily secretion: 100 cc. of 2.92% HCl were diluted to 300 cc. and given through a stomach tube each night at 8 P.M. This was the amount of acid calculated to be present in 1500 cc. of gastric juice at an acidity of 50° C. free HCl. No discomfort was occasioned by this dosage. The patient's condition grew gradually worse with increasing stomatitis, dermatitis, diarrhea up to 7 stools daily and increasing mental confusion. On January 4, 1935, her condition was alarming after 3 weeks of acid therapy, and acid was discontinued. On this day, and for 11 subsequent days, she was given gastric juice in amounts varying from 180 to 300 cc. daily at 8 P.M. By January 8, her stomatitis was much improved, diarrhea reduced to 2 stools daily and the moist dermatitis was drying. On January 13, she developed an acute upper respiratory infection which caused fever for 17 days. In spite of this her pellagrous manifestations improved rapidly, so that on January 16, the day after treatment with gastric juice was discontinued, it was noted that stomatitis was healed, dermatitis desquamating and diarrhea absent. The mental state was much improved. From this time improvement was gradual, with slow resolution of dermatitis and improvement in the mental condition. The patient was hospitalized until March 13, constantly on pellagra-producing diet, in an effort to provoke an early relapse. At the time of discharge all pellagrous manifestations had been absent for 1 month, and weight had increased to 89 pounds. The hemoglobin was 50%; R.B.C., 2,300,000; W.B.C., 6250.

TABLE 4.—ANALYSES OF GASTRIC CONTENTS.

Date.		Free HCl.	Total acidity.
1934.			
Dec. 18	0	8
24	0	3
1935.			
Jan. 1	0	5
9	0	5
16	0	5
21	0	7
Feb. 2	0	7

Weekly examinations, from February 9 to date of discharge, showed no change in the gastric contents.

CASE 5.—(No. 97426.) V. D., a negress, aged 38, was admitted, June 15, 1935. No history was ever obtainable. She was emaciated, weighing 76 pounds, and was comatose, with extensive dermatitis of the hands, wrists, forearms, elbows and feet. A vaginitis was thought to be of pellagrous origin. There was ulcerative stomatitis with salivation and marked glossitis with atrophy of the papillae. General physical examination showed no gross abnormalities other than evidences of extreme dehydration. The urine was concentrated, contained albumin and hyalin casts, acetone and diacetic acid. Stools were frequent and involuntary; no parasites were found. The blood contained hemoglobin, 70%; R.B.C., 3,300,000; W.B.C., 6800. Blood chemical determinations showed slight increase in non-protein nitrogen on admission. No other abnormal findings. The Wassermann and Kahn tests were negative. Temperature, 100.8° F.; pulse, 120; respiration, 40.

This patient was apparently *in extremis* on admission. She was given a liquid, high-caloric, high-vitamin diet, including 45 gm. of dried brewers' yeast. To this was added 12 cc. of dilute HCl; 1 cc. of liver extract (Lilly, 343-soluble) was given intramuscularly daily. In addition, she was given

10 gm. of ventriculin, 3 times daily, for 2 weeks and for another 2 weeks, 90 cc. of liver extract for oral administration daily. Gastric juice in amounts varying from 100 to 300 cc. was given on 49 of the 51 days of observation. All usual measures for emergency hydration were practised on admission and glucose was administered on many occasions; 300 cc. of blood were given by transfusion on July 13, and again on July 19. This patient remained stuporous or delirious during her entire stay in the hospital. She was constantly and increasingly febrile, temperature reaching 105° F. 50 days after hospitalization. Diarrhea was constant and involuntary. Feeding was always forced and usually by tube. Death occurred on August 5, 51 days after hospitalization. *Autopsy* showed no cause for fever or death. There were the usual atrophic changes in the gastrointestinal tract which are seen in fatal pellagra.

TABLE 5.—ANALYSES OF GASTRIC CONTENTS.

Date.	Free HCl.	Total acidity.
1935.		
June 15	4	7
July 21	16	65

Comment. Observation of similar febrile stuporous cases of pellagra led us to expect an early fatal outcome. All known methods of treatment were employed, and have been previously employed by us except the use of gastric juice. It is a question whether the prolongation of life in this instance was due to gastric juice.

CASE 6.—(No. 97541.) A negress, aged 47, was admitted, June 21, 1935. No definite onset of symptoms could be determined. She had been in failing health for 7 months, with increasing weakness, loss of weight and sore mouth. She was very thin, weighing 103 pounds. There was typical pellagrous dermatitis of the hands, wrists, elbows and knees. The tongue was red and smooth, not ulcerated; there was moderate stomatitis. Diarrhea was absent. Mentality was very poor but not definitely deteriorated. The urine was not abnormal. The stools contained no parasites. The blood contained hemoglobin, 70%; R.B.C., 4,232,000; W.B.C., 5400. Blood chemical determinations were normal. Wassermann and Kahn tests were negative. The temperature was 98.4° F.; pulse, 80; respiration, 20.

TABLE 6.—ANALYSES OF GASTRIC CONTENTS.

Date.	Free HCl.	Total acidity.
1935.		
June 22	0	10
July 4	0	0
12	0	10

Subsequent analyses at weekly intervals showed no change in values.

This patient was put on pellagra-producing diet for 2 weeks. No significant change in her condition occurred. On July 4, gastric juice was started and was administered in amounts varying from 80 to 200 cc. for 23 consecutive days. There was steady but not spectacular improvement. On July 20, stomatitis was healed, and the tongue had assumed a normal appearance, dermatitis was exfoliating but not healed. On July 30, when gastric juice was discontinued, all signs of pellagra had disappeared; the weight was 116 pounds. The blood showed some improvement; hemoglobin, 80%; R.B.C., 4,600,000; W.B.C., 9250. Pellagra-producing diet was continued until discharge, on August 7, 1935.

Summary. Six cases of pellagra have been treated with gastric juice in varying amounts given over periods of 10 to 49 days. In 1 instance (Case 1), ground raw beef was incubated with the gastric juice and the predigested beef administered daily for 10 days. Three cases (Cases 2, 3 and 4) of severe pellagra improved more rapidly than our experience would lead us to expect even when optimum diet fortified with vitamin B₂ is administered. One case⁶ of moderately severe pellagra improved rapidly and was in complete remission after 23 days. One case⁵ of extremely severe febrile comatose pellagra survived for 51 days with the administration of gastric juice. All patients except Case 5 were fed a pellagra-producing diet.

Certain variations, interesting but quite inconstant, were noted in the acidity of the gastric juice during treatment.

Conclusions. The results obtained by administering gastric juice to a small number of pellagrins maintained on pellagra-producing diet would indicate that unusually rapid recovery may take place under this treatment.

It is suggested that there is an intrinsic factor present in normal gastric juice which makes possible the utilization of minimal amounts of extrinsic factor (B₂).

Prolonged remission in at least 2 instances indicates that this intrinsic factor may be stored in the body.

The hypothesis is, therefore, advanced that in pellagra there is an intrinsic deficiency of variable degree. Some individuals retain enough intrinsic factor to recover even on diets grossly deficient in vitamin B₂. Others are able rapidly to regenerate intrinsic factor in the presence of an abundant supply of extrinsic factor and so recover on high-vitamin feeding. Others are totally lacking in intrinsic factor and unable to regenerate it even under optimum dietetic therapy. These may recover under substitution therapy with intrinsic factor or may die of nervous or cardiac damage inflicted before therapy was started.

It is further suggested that the intrinsic factor is exhausted or cannot be regenerated during prolonged deprivation of extrinsic factor.

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STUDIES IN DIABETES MELLITUS.

IV. ETIOLOGY. PART 2.*

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Build and Diabetes. Child and adult diabetics show distinct differences, as compared to healthy individuals of the same ages, in regard to build, and this phase must be discussed separately for the two groups.

Height. The adult diabetics have a normal distribution in regard to height (Table 9). The average height without shoes† was 5 feet, 7.2 inches for men and 5 feet, 1.8 inches for women. These measurements are not significantly different from the average heights, with shoes, for males of 5 feet, 8¼ inches, and for females of 5 feet, 4½ inches, based on recent insurance data on heights.²¹ Allowance must also be made for the fact that the diabetics include a large percentage of foreign-born Jewish patients who tend to be below average height, and also a large proportion of old persons who have already suffered some loss in height due to age.

In children, on the other hand, the height at onset tends definitely to be above the average, so much so that overheight may be con-

* Part 1 appeared in the June issue of this journal.

† Where measurements were taken with shoes, deductions for heels were: 1 inch for men and 2 inches for women.

sidered a distinct characteristic of the diabetic child at the beginning of his diabetes. Before presenting results, it may be well to point out the special precautions which are necessary in analyzing these facts for children. First of all, since we are dealing with the period of active growth, the facts regarding the build of the child are trustworthy only if accurate and periodic records of the child's growth are kept or if the onset of the disease can safely be placed within a very short time of the first examination at which accurate measurements are made. In our analysis given in Table 10 we have included only cases where the height as of the date of onset

TABLE 9.—HEIGHT (WITHOUT SHOES) OF ADULT DIABETICS. PERCENTAGE DISTRIBUTION OF PATIENTS AGED 20 AND OVER AT ONSET. BY SEX.
EXPERIENCE OF E. P. JOSLIN, 1897-1928.

Males.			Females.		
Feet.	Inches.	Per cent of total.	Feet.	Inches.	Per cent of total.
Total		100.0	Total		100.0
5	2 and under	4.2	4	8 and under	2.3
5	3	4.3	4	9	3.0
5	4	7.1	4	10	6.1
5	5	11.4	4	11	8.2
5	6	12.7	5	0	11.6
5	7	14.1	5	1	13.4
5	8	14.6	5	2	15.8
5	9	11.7	5	3	13.7
5	10	8.4	5	4	10.5
5	11	6.1	5	5	7.2
6	0	2.9	5	6	4.3
6	1	1.3	5	7	2.2
6	2 and over	1.2	5	8 and over	1.7
Average height: 5 feet, 7.2 inches			5 feet, 1.8 inches		
Number of cases					
with known heights: 2,299			2,381		

was stated, and was consistent with other (usually later measurements), or, if the height was not given as of onset, the case was used only if diabetes was diagnosed within 2 months of onset. Of 159 boys whose diabetes began before age 20, and who met these specifications, 55.3% were above average height for their age, 16.4% were average height and only 28.3% below average height.* Similarly, of 107 diabetic girls, 58% were above average height, 11.2% of average height and only 30.8% below average height. In girls the proportion of tall height was larger under 15 than over that age.

* The figures cited here are much lower than those previously reported by White for this experience. It is due to the use of severer standards of selection of cases and also of more recent height standards which give higher figures for normal than those used by White.

The standards used were relatively severe, namely, Baldwin's²² averages of Iowa children at ages under 6 and a group of private school children at ages 6 and over, on whom successive measurements were available over a period of years. A high frequency of overheight in diabetic children at onset was first pointed out by Priscilla White²³ and since has been reported by many observers. John²⁴ has recently summarized these data.

TABLE 10.—NUMBER OF CASES BELOW AND ABOVE AVERAGE HEIGHT. MALE AND FEMALE CHILD DIABETICS. BY BROAD AGE GROUPS AT ONSET.
EXPERIENCE OF E. P. JOSLIN, 1897-1932.

Age at onset (nearest birthday).	Males.				Females.			
	All heights.	Below average height.	Average height.	Above average height.	All heights.	Below average height.	Average height.	Above average height.
All ages	159	45	26	88	107	33	12	62
Under 5	29	7	5	17	18	4	3	11
5-9	46	14	6	26	26	7	4	15
10-14	53	17	7	29	40	8	3	29
15-19	31	7	8	16	23	14	2	7

Maximum Weight Prior to Diabetes. The adult diabetic tends definitely to be overweight at the onset of his disease. The analysis of this experience (Table 11) is based on the per cent departures from average weight, height and age considered, at maximum weight prior to diagnosis of diabetes.* Among males, age 20 or over at onset, 78.5% were at least 5% overweight at the time of their maximum weight and among women, no less than 83.3%. Moreover, 51% of the males and 59.3% of the females were at least 20% overweight, and 16.5% of the males and 25.8% of the females were actually 40% or more above average weight.

This factor of obesity at or prior to onset is one of the most stable characteristics in the medical history of diabetics. When analyzed in four different periods, the proportion of overweights was approximately the same in all four. Among adult males, the proportion 5% or more overweight varied only between 78.1 and 80.1%, and among females, between 80.5 and 86.4%.

Among patients with onset of diabetes in adult life, the proportion who were overweight at their maximum weight is fairly constant at the various ages (Table 11). The only exception is in early adult life, where 59.2% of males were overweight and 64.6% of females, as compared with 78.4 to 84.6% of males in later life and 81.2 to 88.2% in females.

* As we have indicated in the preceding paper,²⁶ these percentages based on departures from average weight, understate both the frequency and degree of overweight, because these basic averages increase with age. The nature of these increases is such that the average weights at the older ages do not represent the "ideal" weights. Unfortunately, there are no commonly accepted weight standards of that type.

In all these groups, the majority of the remaining cases were of average weight at their maximum. Very few had always been thin people, *i. e.*, at least 20% underweight. Less than 1% were in this group among patients 35 years or over at onset, the proportion being especially small in the case of females. This figure for those 20% or more underweight compares with 1.7%²⁷ among insured men at the time of acceptance for insurance. The latter figure, however, is somewhat too low for the general population, because some marked underweights are rejected for insurance.

TABLE 11.—MAXIMUM WEIGHT PRIOR TO ONSET OF DIABETES OF ADULT DIABETICS. PERCENTAGE IN GROUPS CLASSIFIED BY DEVIATION FROM THE AVERAGE WEIGHT FOR HEIGHT AND AGE. CLASSIFIED BY YEAR OF EXAMINATION, AGE GROUPS AT ONSET AND SEX. EXPERIENCE OF E. P. JOSLIN, 1897-1928.

	Total.	Year of examination.					Age at onset.				
	1897 to 1928.	1897 to 1914.	1915 to 1919.	1920 to 1924.	1925 to 1928.	20 to 34.	35 to 44.	45 to 54.	55 to 64.	65 and over.	
MALES:											
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	
Overweight, total	78.5	79.6	80.1	78.2	78.1	59.2	80.0	81.6	83.3	78.4	
20% or more	51.0	52.2	51.1	49.8	51.8	29.5	51.5	59.8	54.6	51.2	
40% or more	16.5	15.9	16.0	16.1	17.0	10.6	15.6	21.5	14.7	16.3	
30% to 39%	13.9	17.8	13.4	13.1	14.2	5.7	16.5	14.0	16.9	16.9	
20% to 29%	20.6	18.5	21.7	20.6	20.6	13.2	19.4	24.3	23.0	18.0	
5% to 19%	27.5	27.4	29.0	28.4	26.3	29.7	28.5	24.8	28.7	27.2	
Normal weight	13.6	13.4	9.6	14.2	14.4	20.8	13.5	10.9	11.3	15.7	
Underweight, total	7.9	7.0	10.3	7.6	7.5	20.0	6.5	4.5	5.4	5.9	
5% to 19%	7.1	6.4	9.3	6.7	6.8	19.0	5.7	3.8	4.8	4.7	
20% or more	0.8	0.6	1.0	0.9	0.7	1.0	0.8	0.7	0.6	1.2	
FEMALES:											
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	100.0	
Overweight, total	83.3	86.4	80.5	84.6	82.4	61.6	83.9	88.2	85.7	81.2	
20% or more	59.3	75.4	57.2	60.6	57.6	40.0	61.0	65.6	59.7	50.0	
40% or more	25.8	28.8	30.1	25.5	24.8	18.2	32.4	29.7	22.8	14.7	
30% to 39%	14.2	19.2	10.0	15.1	14.1	10.9	14.9	15.6	14.1	12.8	
20% to 29%	19.3	27.4	17.1	20.0	18.7	10.9	16.7	20.3	22.8	22.5	
5% to 19%	24.0	11.0	23.3	24.0	24.8	21.6	19.9	22.6	26.0	31.2	
Normal weight	10.4	6.8	11.9	8.8	11.7	17.5	9.3	8.1	10.9	11.0	
Underweight, total	6.3	6.8	7.6	6.6	5.9	17.9	6.8	3.7	3.4	7.8	
5% to 19%	5.5	6.8	7.1	5.7	5.1	15.1	6.3	3.5	2.7	6.9	
20% or more	0.8	...	0.5	0.9	0.8	2.8	0.5	0.2	0.7	0.9	
NUMBER OF CASES:											
Males	2,251	157	313	793	988	345	471	716	501	172	
Females	2,315	73	210	896	1,166	285	413	802	597	218	

Patients with onset of diabetes between ages 20 and 35 show an appreciably lower proportion of overweights than those with later onset. The frequency of overweight, even in these younger cases, however, is far above normal. Of the males, 59.2% had been overweight at their previous maximum weight and 64.6% of the females. A large percentage of these cases, moreover, was only moderately overweight. The remaining cases were about evenly divided between normal weight and underweight. Even among these patients, between 20 and 35 years at onset, however, relatively few had been markedly underweight (20% or more). Only

1% of these young male diabetics and 2.8% of the females had always been that much underweight.

Comparison With Other Experiences. The presence of obesity prior to the onset of diabetes is probably the best-known characteristic of the disease. It is, therefore, unnecessary to present in any great detail the findings of other observers. In Table 12 we show, therefore, only 3 other recent experiences,^{28,29,30} in comparison with the present one. The basis of the comparison is the percentage of adult patients at least 20% overweight and the percentage at least 30% overweight at the maximum prior to diagnosis of diabetes. It is notable that 2 of the 3 show considerably higher percentages of overweights prior to diabetes than the present one and the lower incidence of overweight in the third group is probably due to the inclusion of a fairly high percentage of children among whom, as we shall see later, obesity is relatively uncommon. A striking feature in all experiences is the greater frequency of overweight among diabetic women than men.

TABLE 12.—MAXIMUM WEIGHT OF ADULT DIABETICS PRIOR TO DIAGNOSIS. PERCENTAGE OF PATIENTS AT LEAST 20% AND AT LEAST 30% OVERWEIGHT. BY SEX. RECENT CLINICAL EXPERIENCES.

	Per cent.			
	20% or more overweight.		30% or more overweight	
	Males.	Females.	Males	Females.
Joslin	51.0	59.3	30.4	40.0
John ²⁸	76.0	78.8	56.1	68.2
Adams ²⁹	68.8*	...	51.9*	...
Palmer ^{30†}	40	52	24	30

* Both sexes combined.

† Includes children.

Weight of Jewish Patients. In Jewish adult patients, the tendency to obesity is even more marked than among other patients. The proportion of diabetic Jewish men who were overweight at their maximum prior to diagnosis was 86.8%, compared with 78.5% for all adult males in this experience. Among Jewish women, no less than 94.3% were overweight at their maximum, compared with 83.3% for all female diabetics. More of the Jewish patients were very stout, particularly the women. Of the diabetic Jewish men, 58.4% were at least 20% overweight as against 51% for total males, and of the Jewish women, 77%, compared with 59.3% for total females. The proportion of the actually obese (40% or more overweight) was about the same for the Jewish men (16.2%) as for all males in this experience (16.5%). Among Jewish women, however, 33.5% were obese, compared with only 25.8% for all

of the diabetic women. The majority of the remaining Jewish patients were of average weight. Only 2 of the Jewish adult patients had always been thin, 1 male and 1 female, both of whom were under age 35 at onset.

The excessive proportion of overweights among Jews is found at every age. The excess is particularly large, however, among patients with onset between ages 20 and 45. As in the case of non-Jewish diabetics, however, the proportion of Jewish patients who had been previously overweight was lower for those with onset at ages 20 to 35 than at later ages.

TABLE 13.—WEIGHT OF CHILD DIABETICS UNDER AGE 20 AT ONSET OF DISEASE. BY SEX AND AGE. EXPERIENCE OF E. P. JOSLIN, 1897-1932.

Sex; age at onset.	Per cent.					Total number of cases.
	Overweight.		Average weight.	Underweight.		
	Moderate.	Slight.		Slight.	Moderate.	
MALES:						
Total	9	9	48	20	14	100
Under 5	4	18	64	14	..	22
5- 9	11	..	59	15	15	27
10-14	13	11	37	18	21	38
15-19	8	31	46	15	13
FEMALES:						
Total	12	10	32	28	18	76
Under 5	15	54	23	8	13
5- 9	11	5	42	21	21	19
10-14	9	12	23	35	21	34
15-19	40	10	10	20	20	10

Basis of weight classification for overweight and underweight is deviation from average weight.

	Under 5	5 to 9	10 to 19
Slight	4 to 6 pounds	5 to 8 pounds	5 to 14%
Moderate	7 pounds or more	9 pounds or more	15% or more

Weight standards: Under age 5, Woodbury; ages 5 to 19, Baldwin and Wood.²¹

Weight of Children. Diabetics with onset during childhood and adolescence in contrast with older diabetics do not show a high frequency of overweight. Entirely different standards for measuring the degree of overweight are necessary for children, because each pound departure from average weight may represent a deviation of as much as 4%. On the basis of the standards adopted, which are described in Table 13, 48% of the diabetic boys and 32% of the girls were average at their maximum. Moreover, there were twice as many who were underweight as were overweight, both among boys and girls. Excessive weight was relatively infrequent.

The details are shown separately for 5-year age periods in the table. They show some variations from the general situation described, but these differences are not consistent and seem to be due to the small number of cases involved. Joslin, Root and White,²³ Boyd and Nelson,³² Spencer³³ and others report similar results in their series of diabetic children.

The difference in the build picture of child and adult diabetics is significant. In the case of the child a vertical overgrowth is typical, whereas in the adult it is lateral. It is likely, however, that these two types of overgrowth correspond and both are believed to be essentially of the same nature, namely, of endocrine origin. Before discussing this aspect of the situation, however, it is necessary to review other pertinent facts in the medical history of diabetics.

Incidence of Thyroid Abnormalities. The most distinct clinical evidence of multiglandular etiology of diabetes is the frequency of thyroid abnormalities, especially hyperthyroidism, among diabetics. These cases have been studied intensively by the senior author since 1921.* At the outset the difficulty of correct diagnosis of diabetes associated with hyperthyroidism must be stressed. Glycosuria and, to a less extent, hyperglycemia are frequent in hyperthyroidism, and it is often hard to tell whether the disturbed metabolism is really diabetic. For this reason it may be advisable to raise the standards of diagnosis of diabetes in hyperthyroidism. In addition, therefore, to the figures based on normal standards, others are shown in the text, in parentheses, in which the level of the blood sugar was at least 0.15 % fasting and 0.2 % after food and with glycosuria also present. On this basis, 1.1 (1) % of the males and 3.3 (3) % of the females, first seen during 1921 to 1928, gave a history of hyperthyroidism or had it when examined. None of these patients was under age 20 when first seen. Among males the proportion of hyperthyroid cases was low at every age, but among females there was a decided peak between the ages of 35 and 44, with 8.2 (7.2) % having a history of hyperthyroidism. Most of the hyperthyroid cases, both male and female, were between the ages of 20 and 54, constituting 1.9 (1.6) % of the total men and 5.6 (5.1) % of the total women in this broad age group. These percentages are believed to be higher than normal, but just how much is difficult to say because no good standards exist by which to measure the normal frequency of hyperthyroidism. It varies from place to place, the so-called "goiter belts" showing high rates. In the northeastern section of the country from which most of these cases are drawn, toxic goiter is not especially prevalent. Figures in the present experience are higher than those reported by most observers,^{30,34,35} but the data are scanty and do not warrant repro-

* In cooperation with F. H. Lahey. This experience since 1921 includes many diabetics among Lahey's surgical thyroid cases and overstates somewhat, therefore, the incidence of such cases among diabetics.

ducing here. John³¹ has summarized some of these experiences. Most of them are in agreement with the present one in regard to the high proportion of diabetic women with hyperthyroidism, as compared with male diabetics. It is significant, moreover, that where goiter generally is most prevalent, the proportion of diabetics with hyperthyroidism is high.

Minor thyroid abnormalities (moderate or marked enlargements; fullness; palpable thyroid and previous thyroid surgery, cause unknown) were much more frequent in this experience than hyperthyroidism. Among males 2.9% and among females 6.8% showed such abnormalities. The proportions tended to be highest during adolescence and early adult life and lower at the older ages. At every age they were higher among females than males. These findings characterize non-toxic thyroid disease generally. The percentage of these cases among diabetics appears to be relatively high, but accurate measurement of the excess is impossible to make because of differences in classification and in geographical distribution of thyroid abnormalities of this type.

Pituitary Gland. There are striking clinical findings which suggest that the pituitary gland may influence the onset or course of diabetes. That diabetic adults are overweight and diabetic children are overheight prior to the onset of diabetes points strongly to the operation of a pituitary factor. It is well recognized that glycosuria and diabetes are extremely common in acromegaly. Furthermore, we know that pituitary extract and insulin are antagonists. When extracts of the anterior lobe of the hypophysis are injected into a normal dog, temporary glycosuria, hyperglycemia and hyperlipemia develop. The work of Houssay³⁵ and his associates is of particular significance. These workers showed that removal of the hypophysis lessens greatly the severity of the diabetes in totally depancreatized animals.

Suprarenal Glands. It has long been understood that the suprarenal glands exert an influence over carbohydrate metabolism. Such knowledge, however, has been concerned largely with the effect of adrenalin, the secretion of the medullary portion of the gland. This substance causes glycogenolysis in the liver, and in this way acts as an insulin antagonist. Attempts to ameliorate severe diabetes by adrenalectomy or section of the splanchnic nerves have had this relationship as a basis.

More recently a new field has been opened up by the work of Long and Lukens,³⁷ who have shown that when bilateral total adrenalectomy is carried out in totally depancreatized cats, the diabetes becomes much milder, resembling that of the hypophysectomized animals in the Houssay experiment. The total adrenalectomy stops the breakdown of protein and abnormal production of ketone bodies which are characteristic of diabetes.

The Incidence of Gall Bladder Disease. Gall bladder disease as

a precursor to diabetes has been reported often in the medical literature. The chief causes suggested are disturbed lipoid metabolism, especially in relation to gall stones, and infection of the gall bladder, subsequently involving the pancreas. In this experience a previous history of gall bladder disease is common among adult diabetics, particularly women. In the period 1897 to 1928, 2.6% of the men gave such a history. Of these, 1.5% had had gall stones and 1.1% inflammation of the gall bladder or other symptoms of gall bladder disease. Women with such histories numbered 7.6% of the total, of whom 4.7% gave a definite history of gall stones and 2.8% had had cholecystitis or other evidence of gall bladder disease. Such histories subsequent to examination were likewise fairly frequent.

The true incidence of gall bladder disease is probably understated by the figures relating to the whole period, for analysis of the data shows that the incidence is higher among patients seen in recent years, probably due to more careful attention to this factor in taking case histories. Thus, in the four years ending in 1928 the proportion with biliary tract disease was 3.6% for men and 9.9% for women, proportions so high as to suggest a close relationship between the two conditions. We must admit, however, that gall bladder disease has not been prominent as a cause of death. In the period 1922 to 1935, of 2415 deaths of diabetics, only 11 were ascribed to gall bladder disease by the attending physician.

Age has a decided bearing on the frequency of gall bladder disease. Among men the proportion is decidedly below the average up to age 45, but then jumps and increases slightly thereafter with advancing age. The proportion is highest in those with onset of diabetes at ages 65 and over, when it reaches 4.6%. Among women, a sharp increase in the proportion of gall bladder cases takes place at age 35, or 10 years earlier than in the case of men. The proportion giving a history of gall bladder disease remains fairly constant thereafter in the case of women. The maximum proportion among them, however, in the whole experience is found between the ages 60 and 65, where 9.7% gave a history of gall bladder disease, but in the period 1925 to 1928 the peak occurred between ages 45 and 50, with 13.3% reporting gall stones or symptoms of biliary disease.

Practically all of the diabetics with a history of gall bladder disease were overweight prior to their diabetes. Of the 71 males, only 7 were within normal limits at their maximum weight prior to diagnosis, and only 4 underweight, but none as much as 20%. Likewise, among the 219 women with gall bladder disease, only 13 had been average weight at their maximum before diagnosis and only 3 had always been underweight; none of them, however, as much as 20%. The proportion of gall bladder cases among all overweight men, in this experience, was 3.1%, compared with 2.3%

for both normals and underweights. Among women, however, the differential was even larger, with 8.5% of the overweights reporting gall bladder disease, compared to 5.3% for normals and 2% for underweights. The proportion of gall bladder cases among overweights did not show any significant trend in relation to the degree of overweight. The obese reported only a slightly greater proportion of gall bladder cases than the moderate overweights.

Jewish patients did not differ markedly from other patients in the proportion reporting a history of biliary tract disease. There was a slight excess in the case of females. The proportion for Jewish women was 8%, compared with 7.6% for all women during the entire period, 1897 to 1928. In recent years, 1925 to 1928, the proportions were 10.6% and 9.9%, respectively. The weight characteristics of Jewish diabetics with gall bladder histories differs not at all from those observed among all patients with this history.

Despite the high frequency of gall bladder disease among these diabetics, it is questionable whether the figures are really significant. The disease is a fairly common ailment in adult life. In one clinic³³ such conditions were reported in 6% of the patients over age 20. The incidence in serial autopsy studies is about 10 times as high.^{39,40} Stones are present in one-fifth to one-half of these cases, the higher proportions being present at the older ages. Most of these cases, of course, give no symptoms during life. Moreover, gall bladder lesions are notoriously common among the obese and, since most diabetics are overweight before the onset of their disease, a high frequency of gall bladder disease would be expected. Dublin, Jinnenis and Marks,⁴¹ in a study of insured persons with a history of gall bladder disease, all free of diabetes when they were examined for insurance, found a large proportion, especially of the women, to be overweight. In addition, analysis of the subsequent mortality of the group showed a low incidence of diabetes up to the closing date of their study. Beaser,⁴² in a study of Vanderbilt Clinic records, found that gall bladder disease proved by operation or autopsy was equally frequent in diabetic women and a control group, and the proportion of cases with gall bladder disease diagnosed from the symptoms was even greater in the control group. His analysis was limited to ages 40 to 65 and, in the case of the diabetics the gall bladder histories were limited to those preceding the diabetes.

Arteriosclerosis. Arteriosclerosis, resulting in inadequate blood supply to the pancreas, has been suggested as one of the causative factors in diabetes, particularly in the aged. The proneness of the diabetic, especially when inadequately treated, to develop arteriosclerosis prematurely is well known and consequently the incidence of arteriosclerosis among diabetics without regard to the duration of the disease is likely to lead to erroneous conclusions. Consideration may be given, however, to the incidence of arterial change as an etiological factor in those cases which, so far as can be determined,

were of relatively recent origin, that is, diagnosed within 1 year of onset. Analysis has been made of the incidence and degree of sclerosis of the peripheral arteries disclosed by palpation of the radial artery at examination in all such cases in this experience, but the data are most reliable and consistent for cases first seen beginning July 1, 1927, since which date a classification of arterial change based upon Pratt and Bushnell's⁴³ description has been used. This method distinguishes the degree of abnormality of the radial arteries as follows: 0, none; 1, palpable; 2, roll under finger; 3, tortuous; and 4, beaded or pipestem. The last two groups, the severer grades, seem to be comparable with classifications used earlier than July 1, 1927, and these earlier results are used.

TABLE 14.—INCIDENCE AND DEGREE OF SCLEROSIS OF RADIAL ARTERY AT EXAMINATION AMONG DIABETICS SEEN WITHIN 1 YEAR OF ONSET. PER CENT OF CLASSIFIABLE CASES. BY SEX AND AGE GROUPS AT EXAMINATION. EXPERIENCE OF E. P. JOSLIN, 1922 TO 1928.*

Sex; degree of arteriosclerosis.	July 1, 1927 to 1928.							August 7, 1922 to 1928.						
	All ages.	Under 20	20 to 39.	40 to 49.	50 to 59.	60 to 69.	70 and over.	All ages.	Under 20.	20 to 39.	40 to 49.	50 to 59.	60 to 69.	70 and over.
MALES:														
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0							
0	26.2	94.4	37.1	20.0	7.3							
1	24.4	5.6	42.9	37.1	23.6	22.5	10.0							
2	29.5	...	14.3	37.2	50.9	40.0	15.0							
3	14.9	...	5.7	5.7	16.4	30.0	40.0	11.9	...	1.3	8.4	15.1	26.4	43.9
4	5.0	1.8	7.5	35.0	4.0	0.9	2.6	9.4	29.3
FEMALES:														
Total	100.0	100.0	100.0	100.0	100.0	100.0	100.0							
0	44.9	94.9	75.7	51.2	21.3	11.9	7.1							
1	28.0	5.1	21.6	37.2	41.0	31.0	14.3							
2	22.0	...	2.7	11.6	32.8	42.8	57.2							
3	4.7	4.9	14.3	14.3	6.9	1.6	8.6	18.3	17.5
4	0.4	7.1	0.4	0.5	0.8	2.5
NUMBER OF CASES CLASSIFIABLE:														
Males	221	36	35	35	55	40	20	674	118	150	107	152	106	41
Females	236	39	37	43	61	42	14	711	120	111	122	187	131	40

* Classification based on Pratt's description since July 1, 1927. Data prior to that date comparable only for Grades 3 and 4.

The analysis in Table 14 of cases with diabetes of less than 1 year's duration who were first seen after July 1, 1927, shows that among 221 males, 26.2% were free of arterial change; 24.4% had Grade 1 abnormalities; 29.5%, Grade 2; 14.9%, Grade 3; and 5%, Grade 4. Among 236 females, arteriosclerosis was less frequent, particularly the severer grades. Actually 44.9% of these women had normal arteries; 28.0% had Grade 1 abnormalities; 22.0%, Grade 2; 4.7%, Grade 3; and only 0.4%, Grade 4.

In both sexes, practically all the patients under age 20 with diabetes of less than 1 year's duration were free from any signs of arteriosclerosis, only 4 out of 75 cases showing Grade 1 abnormalities

and none, of any greater degree. This picture changes very rapidly with age, however, particularly among males. Every male diabetic past 60 showed abnormalities of at least Grade 1, and the proportions with changes of Grades 3 or 4 reached 18.2% among those patients between 50 and 59, 37.5% at ages 60 to 69 and 75% at ages 70 and over. Among females, the percentages were much lower. Indeed, 21.4% of the diabetic women 70 or over at examination had no or slight abnormalities of the radial arteries and a like proportion, severe abnormalities (Grades 3 and 4). The figures on severer types are confirmed by the more extensive series of observations based on all first-year cases seen from the beginning of insulin treatment in 1922 down to the end of 1928.

The figures for these diabetics display the usual age relationships in arterial changes, but they are far above normal, particularly in the case of males. Comparison with supposedly typical samples in the population is not altogether accurate, however, because of differences in standards used, and this limitation should be kept in mind in the comparisons that follow. Sydenstricker and Britten⁴⁴ found that the percentage of males with normal arteries was 88.6% at 20 to 24; 83.6 at 30 to 34; 72.3 at 40 to 44; 56.1 at 50 to 54; and 43 at 60 to 64. By far the largest proportion of those with arterial thickening showed very slight abnormalities and even between 60 and 64 only 18.6% showed moderate or marked thickening. In their series,^{44,45} practically no sex differences were found in the percentage showing arterial thickening, whereas among these diabetics, the male rates were distinctly higher than those for women. Because diabetics are generally overweight before onset of their diabetes, it is fairer to compare the frequency of arterial change among them with that of a typical series of overweight persons, but unfortunately such data on overweights are unsatisfactory because the usual method of palpating the radial artery leads to understatement of the arterial changes in fat persons. As a result, in the series⁴⁶ reported by Britten, as well as in another series reported by Dublin, Fisk and Kopf,⁴⁷ arterial thickening was found more frequently among the underweights than overweights. This is contrary to the actual situation as revealed by the statistics on build in relation to mortality from causes which are of arteriosclerotic origin.

Obviously, however, data on changes in the peripheral arteries are at best only a rough index to arteriosclerosis elsewhere in the body and, more particularly, in the pancreas. The concept of a truly generalized arteriosclerosis is largely discredited today. Moreover, although sclerosis of the arteries of the pancreas is involved in a considerable percentage of the cases, it is not necessarily diffuse or severe enough to interfere seriously with the function of the organ. Reliable data can only be secured from autopsy studies. Among 259 diabetic deaths in the present series in which the pancreas was available for study at autopsy, Warren⁴⁸ reported marked

arteriosclerosis of the pancreas present in only 5%. This figure includes cases of all durations of diabetes and it is likely that the condition is even rarer in newly developed cases. Warren's figure is much lower, however, than that of Wartman,⁴⁹ who, for a general experience, reported marked arteriosclerosis of the pancreas in 22.3% of the cases at all ages and at ages past 60, in 45.7% of the men and 31.8% of the women. Root and Sharkey⁵⁰ compared 175 diabetic and 175 non-diabetic autopsies and found that patients with diabetes of less than 1 year's duration showed no more arteriosclerosis than non-diabetic cases of similar age. On the other hand, diabetics of longer duration showed far more extensive arteriosclerosis than non-diabetics.

The wide differences in the figures quoted make it difficult to draw any positive conclusions on arteriosclerosis as an etiological factor in diabetes, despite the high incidence of peripheral arteriosclerosis in diabetes, particularly among males. The picture is rather confused. One can say definitely, however, that arteriosclerosis is not a factor in the causation of diabetes in childhood, and very improbably a factor in adults up to age 40. After that age, the question is still open and further investigation is necessary to clarify it.

Cancer of the Pancreas. Cancer of the pancreas is undoubtedly a cause of diabetes in a small proportion of cases. Among patients first seen between 1897 and 1928, there have been 28 who had primary cancer of the pancreas, and 1 patient with a secondary cancer of the pancreas. They constituted 13.4% of all patients with cancer, as compared with 2%* in the general population. The full importance of cancer of the pancreas is unknown, because it is not usually diagnosed at the time of examination for diabetes.

Summary. 1. A representative group, of 6357 private diabetic patients (treated by Joslin in the office or hospital or by consultation over a period of 30 years) and of 463 diabetic children seen more recently, is described together with an analysis of various etiological features of the disease, which lend themselves to statistical interpretation.

2. The residence of 85% of the patients was in New England, 67% in Massachusetts, 41% in the Boston Metropolitan District and 14% in Boston itself.

3. American nativity characterized approximately two-thirds of the adult patients; one-sixth of the patients were Jews, although but one-twelfth of the population in the area from which they came was of that race.

4. Occupations were diverse, but there was a rather large proportion of proprietors, officials, managers and members of professions. Physicians alone amounted to 6.9% of 2304 patients whose occupations were definitely recorded.

* Based on deaths only.

5. Most of the patients were first examined because of symptoms of diabetes, but a large number were diagnosed as a result of routine examinations. Insurance was the chief of these and accounted for the recognition of 12.6% of the males. The number of cases diagnosed after application for insurance has steadily increased.

6. Males exceeded females until 1922, but since that date the situation has been reversed and the disparity is definitely increasing.

7. The number of cases increased steadily from infancy to a maximum at ages 50 to 54, except for a slight dip in the late teens, and dropped rather sharply from the peak in old age. There has been a definite increase in recent years in the proportion of patients at the older ages: past 60 among males and past 50 among females. Comparative data are given for other diabetic series. Analysis with regard to the true incidence of age at onset of diabetes shows that onset is most frequent in the sixth decade, and next highest in the seventh decade.

8. Jewish patients develop diabetes relatively young. The median age at onset of the Jewish patients was more than 2 years younger than that of all patients. Jewish female patients exceeded the males up to the end of 1928 by 46.3% and in the late forties and fifties, by nearly 2 to 1.

9. The present series of cases partially confirms the New York City data of Mosenthal and Bolduan, which show that the incidence of diabetes in married women is higher than in single women. No difference, however, was found between single and married men. The frequency of onset among women in the late forties or fifties reflects the strain on the endocrine system during menopause when gain in weight is also usual.

10. The height of diabetic children at onset tends definitely to be above average, but there is a normal distribution of height of diabetic adults.

11. The weights of adults in this group at onset of the disease were definitely above standard. Among males age 20 or over at onset, 78.5% were at least 5% overweight at the time of their maximum weight, and among women, no less than 83.3%. In children and adolescents, on the other hand, twice as many were underweight as overweight.

12. In Jewish adult patients, the tendency toward obesity was even more marked than among other patients. Of the Jewish men, 86.8% were overweight and 94.3% of the Jewish women.

13. Hyperthyroidism was present in 1% of the males and 3% of the females first seen during 1921 to 1928.

14. The influence of the pituitary and adrenal glands upon diabetes is discussed.

15. A history of biliary tract disease was reported by 3.6% of the men and 9.9% of the women first seen in 1925 to 1928. Practically all of the diabetics with gall bladder disease were overweight.

16. Arteriosclerosis was practically absent in diabetics under age 20 whose diabetes was of less than 1 year's duration. It increased with advancing age until at ages 60 and over every male diabetic exhibited it in some degree.

17. Cancer of the pancreas is a cause of diabetes in a small percentage of cases.

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TREATMENT OF DIABETIC COMA.

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A CONSIDERABLE mortality still exists in patients with diabetic coma, despite the introduction of insulin. In a recent series of cases of diabetic coma treated in Joslin's Clinic, Marble, Root and

White¹ report a mortality of 11%. Eight deaths similar to those reported by the above authors have occurred in this hospital since 1928.* We believe that death in these cases was due to the loss of a large part of the alkali reserve of the body (mainly sodium) and that its replacement would have reduced the mortality considerably.

All investigators now agree upon the general principles involved in the treatment of diabetic coma, since insulin has become the major tool in the treatment. Of primary importance is the relief of the organic acidosis, or ketonemia, brought about by incomplete oxidation of fats; which, in turn, is the result of insufficient oxidation of carbohydrate. We are concerned, then, at the moment, with the presence of the ketonemia and not the hyperglycemia. Hyperglycemia, *per se*, is never the immediate cause of death nor the cause of serious symptoms. The only known detrimental effect of hyperglycemia is a temporary reduction in the inherent ability of the organism to utilize glucose. The only immediate reason for oxidizing glucose is to promote complete oxidation of fat. This is accomplished by the use of sufficient amounts of insulin. Thus, the ketonemia can be abolished.

The other important disturbance, dehydration, which has resulted from lack of fluid intake, vomiting and acidosis, is combated by the administration of large amounts of fluid, usually in the form of physiologic saline parenterally. These measures (administration of sufficient insulin and fluid) are usually successful in the treatment of diabetic coma.

But the occurrence of another state, which if not recognized and treated will quickly end fatally, demands attention. This condition should always be suspected when the signs of acidosis and coma persist after ketonuria has been abolished. These are the cases which are commonly called "insulin resistant" or are said to have been in coma too long to permit the possibility of recovery.

Broadly, what may cause acidosis? Normally, the pH of the blood plasma is 7.4† At this pH there are 20 parts of base bicarbonate (BHCO_3) to each part of carbonic acid (H_2CO_3) in the blood plasma.² Base (B) represents a total of the basic elements in the blood (Na, K, Ca, Mg) of which sodium makes up over four-fifths.

Thus, we have the equation
$$\frac{\text{BHCO}_3}{\text{H}_2\text{CO}_3} = \frac{20}{1} = \text{pH } 7.4.$$

* It is not the purpose of this paper to present a statistical report of cases treated in the manner outlined. It is desired to express a point of view and to indicate the scientific data available in its support.

† Simply stated, pH is a negative logarithmic designation of the hydrogen-ion concentration of the fluid or solution considered. Thus the logarithmic designation of 7 is an abbreviation for 10^{-7} or 0.0000001. In the case of hydrogen-ion concentration this means 1 gm. of hydrogen ions in 10 million gm. of water. Water is very slightly ionized. Since the number of hydrogen ions necessarily equals the number of hydroxyl ions, water is neutral. The concentration of either hydrogen or hydroxyl ions in pure water is 10^{-7} . This represents a pH of 7 or a p(OH) of 7.

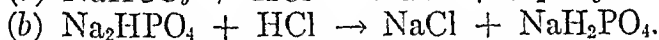
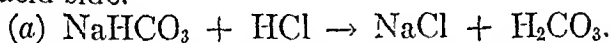
It is obvious that anything which causes a decrease in BHCO_3 or an increase in H_2CO_3 will cause a shift of the pH of the blood toward the acid side. This is expressed in the Henderson-Hasselbalch equation $\text{pH} = 6.1 + \log \frac{\text{BHCO}_3}{\text{H}_2\text{CO}_3}$.

1. *Increase in H_2CO_3 .* This condition is found in patients where there is interference in the gaseous exchange in the lungs, as, for example, in bronchial asthma or emphysema of the lungs. The symptom complained of is dyspnea on exertion because a sudden increase of carbon dioxide to be disposed of rapidly cannot be adequately driven out of the lungs. Thus there is an increase of H_2CO_3 of the blood. This, of course, represents a mild degree of acidosis.

2. *Decrease in NaHCO_3 .* This may occur in one of two ways: (1) A direct loss of NaHCO_3 from the body, such as occurs in diarrhea, will lower the total alkali of body; (2) a replacement of the bicarbonate ion (HCO_3) by an increase of other acid radicals—such as chlorid, phosphate, sulphate, lactate or the incompletely oxidized fatty acids diacetic or beta hydroxybutyric—will lower the total amount of NaHCO_3 .

What are the normal defense mechanisms of the body for the prevention of acidosis? There are three main defenses: the blood buffer system, the pulmonary system, and the renal system.

1. *Buffer System.* The sodium bicarbonate (NaHCO_3) and sodium phosphate (Na_2HPO_4) buffer system, in the presence of a strong acid, act by the formation of a weak acid and a neutral salt. This allows the pH of the blood to shift only very slightly toward the acid side.



Protein, being an amphoteric substance, may act as an acid or a base, depending upon its environment. As the pH of the blood shifts toward the acid side, less and less of the protein acts as an acid, thus liberating base to combat the acidity.

2. *Pulmonary System.* When a strong acid enters the body it causes the decomposition of NaHCO_3 to make its own sodium salt and liberates carbon dioxide. The lungs then increase their ventilation to expel the newly formed carbon dioxide and in addition rid the body of some of the preëxisting carbon dioxide. This prevents the pH of the blood from dropping as low as it would if the preëxisting carbon dioxide had remained constant. This mechanism adjusts for finer changes in pH but becomes inadequate for large changes.

3. *Renal System.* In severe acidosis the buffer and pulmonary systems are overtaxed and become inadequate and renal activity comes into play. There are two important functions of a normal kidney in the face of severe acidosis, as is well shown by the work of Gamble, Ross and Tisdall:³ (1) A normal kidney is able to secrete urine at a pH of 5. In the stage of activity 5% of the diacetic

acid and 20% of the beta-hydroxybutyric acid pass unneutralized by base, thus conserving base. (2) The kidney begins to manufacture ammonia so that the acid radicals may be excreted as ammonium salts; thus also conserving base. In this way a normal kidney practises base economy.

Let us return now to the question being considered. Having administered fluid to combat dehydration and having given sufficient insulin to completely abolish ketonuria, what is the mechanism for the persistence of all of the signs of acidosis and coma with a continued low CO_2 combining power? Richardson⁴ reports a case with exactly these conditions. He suggests three possibilities in explanation:

1. That loss of base from the body accompanying a severe dehydration results in an alkali deficit.
2. That most of the ketone bodies are excreted in these cases in the form of beta-hydroxybutyric acid. (Our clinical tests show only the presence of acetone and diacetic acid in the urine.)
3. That perhaps the kidney shuts down entirely on the excretion of ketones but that they remain in high concentration in the blood.

Hartmann,⁵ however, has done blood analyses to determine ketone body content in such states and finds a negligible quantity. In some cases he has administered sufficient insulin to bring the blood sugar to hypoglycemic levels. He then finds very little organic acid in the blood but the CO_2 combining power remains low. He states, "It seems apparent, therefore, that much of the base released by organic acid on oxidation is claimed by acid other than carbonic or is excreted from the body." Accordingly, continuation of acidosis and coma is not due to a persistence of ketonemia (organic acidosis).

The difficulty lies in the fact that the last defense of the body, the renal system, has been overwhelmed by the severe acidosis and there has been a continued drainage of base from the body. The alkali reserve of the body has been depleted and a condition of "inorganic acidosis" exists. First, the normal kidney does not begin the manufacture of ammonia in increased quantities until the supply of readily excretable base is diminished; that is, until there is a physiologic need of the body to conserve base. Therefore, from the very onset of acidosis, the body has lost some of its readily available base in trying to excrete the organic acids which were rapidly accumulating. Folling⁶ has shown that in experimental acidosis ammonia excretion is very little accelerated the first day, even though the pH of the blood may fall to 7.1. But later, as the available base falls, ammonia production increases. When ammonia production finally reaches its maximum (about 10 gm. of ammonia in 24 hours) it is not sufficient in amount to prevent further

* The CO_2 combining power represents the "alkali reserve" of the blood and reflects directly the "alkali reserve" of the body.

loss of base because of the very large amounts of organic acids which are being presented to the kidney for excretion.

Finally, the kidney temporarily loses its function to make ammonia or to produce a very acid urine. It is common to note the presence of albumin, casts and red blood cells in the urine of patients in diabetic coma with dehydration. Along with the urinary signs of renal damage there is often a rising blood non-protein nitrogen (N.P.N.), oliguria and sometimes anuria. All of these signs disappear when the acidosis and dehydration are corrected. The injury to the kidney has been attributed by various authors to the accompanying severe dehydration and to the toxic effects of the severe acidosis. Coburn⁷ recognizes and stresses the importance of temporary renal insufficiency in diabetic coma. The reduction in ammonia production, then, allows more sodium to be excreted in combination with eliminated acid radicals. Linder⁸ fed hydrochloric acid to a group of people with normal kidney function and to a group of nephritics and measured the ammonia and sodium excretions in both groups. Invariably the nephritic group excreted much more sodium and less ammonia than did the normal group.

As a final insult oliguria or anuria develops as a result of the dehydration. The kidney is then not able to excrete all of the waste products as is evidenced by the retained N.P.N. in the blood. The other normally excreted inorganic acid radicals, phosphates and sulphates (products of protein metabolism) are also retained. In the blood stream these combine to form their sodium salts at the expense of sodium bicarbonate. If the alkali reserve is then measured by determining the CO_2 combining power of the blood, it is found to be extremely low.

If, besides the mechanisms considered above, the diabetic patient has had some preëxisting renal damage, it is apparent that a much more severe inorganic acidosis might develop. If the alkali reserve is measured in a patient with chronic nephritis and mild renal retention, it is found to be relatively low. In uremia the administration of sodium bicarbonate will often bring the patient temporarily out of the unconscious state and relieve the air hunger.

Therefore, in severe and prolonged diabetic coma with marked dehydration, one is dealing with a total decrease of the sodium of the body and a total increase in the fixed inorganic acids, sulphates and phosphates. Much of the base which was able to be retained in the body is tied up in the form of these inorganic salts at the expense of sodium bicarbonate. Having administered insulin, some sodium is liberated by the disappearance of the ketone acids. But, while a small amount may form sodium bicarbonate, most of the sodium is immediately taken up in combination with the rapidly accumulating sulphates and phosphates.

If, after large quantities of fluid have been given to combat dehydration and the body has been rid of ketone acids by the

administration of sufficient insulin, signs of acidosis (Kussmaul respirations, etc.) and coma continue, the patient is in imminent danger of death. The CO_2 combining power is found to be low and the state of "inorganic acidosis" exists. The pH of the blood must be quickly brought back to normal and the alkali deficit relieved. In this state sodium bicarbonate* should be administered without delay. The response is frequently dramatic. Kussmaul respirations change quickly to a normal type and coma rapidly disappears.

Lemann⁹ observes that recovery from coma usually runs parallel to the rise of the CO_2 combining power and the disappearance of ketonuria. Haines and Davis¹⁰ warmly endorse the use of sodium bicarbonate as an adjunct to insulin and use 1000 to 1500 cc. of a 5% solution by duodenal tube. They have never seen harmful results. Campbell,^{11, 12} and Hartmann⁵ for many years have advocated the use of alkali therapy as an addition to the well established treatment of diabetic coma.

In the recent paper from Joslin's Clinic, referred to above, Marble, Root and White¹ report 55 treated cases of diabetic coma. Six of these patients died in diabetic coma despite the usual treatment. Alkalis are not used in that clinic. Four of the cases died within 4 to 13 hours after admission with low CO_2 combining powers, marked dehydration and shock, oliguria or anuria. The diacetic acid in the urine varied from none to a trivial amount. This we believe to be the small group of cases where there is a definite indication for the use of alkalis.

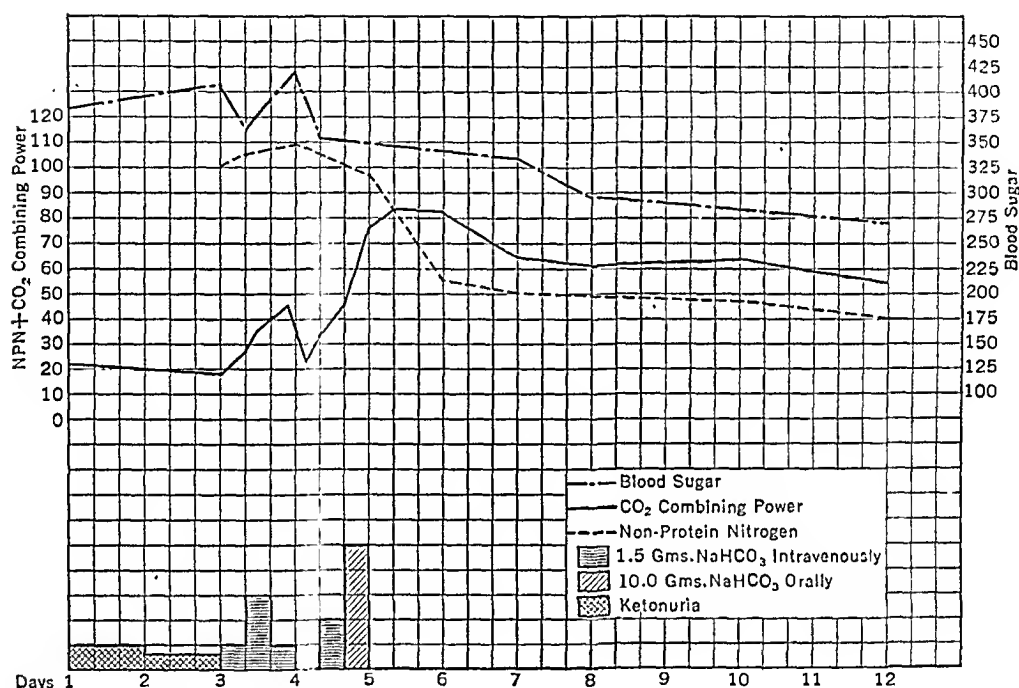
The following case illustrates some of the problems discussed:

CASE 1.—A 55-year-old woman had been known to be diabetic for 3 years before admission. Her diabetes had been uncontrolled over this period. She had lost 80 pounds in weight (210 to 130 pounds). One week before admission both she and her husband had become ill after eating oysters. The husband had abdominal cramps and diarrhea which lasted for 2 days. The patient had nausea, vomiting, abdominal cramps and diarrhea. These symptoms gradually became more marked. For 4 days before admission she retained no food or fluid. Twelve hours after admission she became semicomatose. She had received 10 units of insulin 3 hours before admission to the hospital.

On examination she was found to be deeply comatose. She was severely dehydrated. Respirations were typically Kussmaul. No tendon reflexes could be elicited. The Babinski sign was absent. The urine showed + + + + sugar, + + + + reaction for diacetic acid, ++ albumin, a few red blood cells, and occasional granular casts. The blood sugar was 378 mg. %, CO_2 combining power 21 volumes %, and N.P.N. 100 mg. %. Physiologic saline was administered on admission. She received a daily average of 3500 cc. intravenously for the first 4 days. Thereafter intravenous fluids

* Sodium bicarbonate, 1.5 gm. in 20 cc. of water, can be obtained in sterile ampules ready for intravenous use. A solution of sodium bicarbonate isotonic with the blood contains 13 gm. per liter. The usual dose recommended to bring the CO_2 combining power to normal is 0.5 gm. of NaHCO_3 per kilogram of body weight. If the patient can swallow or a stomach tube is passed, sodium bicarbonate is just as effective this way as intravenously.

were not necessary since she was taking fluids well by mouth. Sufficient insulin was given daily to insure complete combustion of fats, since tests for diacetic acid and acetone in the urine were negative after the second day in the hospital. The patient, however, remained in coma and continued to have Kussmaul respirations after ketonuria had been abolished. On the 3d day she became markedly cyanotic and air hunger became very severe. A CO_2 combining power at this point was found to be 19 volumes %. Three grams of NaHCO_3 in a 7.5% solution were then given intravenously with most dramatic results. Cyanosis disappeared in 15 minutes. Respirations returned to a normal type. The patient became much brighter and was able to talk but was still stuporous. Through the day 4.5 gm. more of NaHCO_3 were given intravenously. As noted on the chart, the CO_2 combining power rose on that day to 45 volumes %.



The following day she was found in the same state of collapse and the CO_2 combining power was 22 volumes %. The same dramatic response followed intravenous administration of 3 gm. of NaHCO_3 . Since the patient could now take fluids by mouth, she was given 1000 cc. of a 5% solution NaHCO_3 (50 gm.) orally over the next 12-hour period. The CO_2 combining power rose to 82 volumes % and gradually came down to the normal level of 55 volumes % by the 12th day. She was able to converse and was improved in all respects. As noted on the chart, the N.P.N. and blood sugar responded satisfactorily. From the 5th day on, the patient was given a diet of milk and cream containing 2000 calories and 100 gm. of available glucose.

This case serves to illustrate the rapid clinical and chemical improvement that may be brought about in a moribund patient when alkali therapy is added to the usual treatment of diabetic coma.

While it is not implied that alkali is necessary in every case of diabetic coma, its routine administration will replace a certain amount of the base which has necessarily been rendered unavailable.

However, in a small group of cases in which the acidosis is severe and the coma has been prolonged, the administration of sodium bicarbonate may be and sometimes certainly is a life-saving measure.

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THE VISCOSITY, PROTEINS AND LIPIDS OF THE BLOOD PLASMA IN ESSENTIAL HYPERTENSION.

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MANY studies have been reported of the viscosity of the blood in hypertensive states, the great majority of the observations having been made upon whole blood. These investigations have demonstrated no consistent relationship between blood viscosity and the presence or degree of hypertension. Since the viscosity of whole blood is influenced by that of the plasma as well as by the number and volume of red blood cells,¹ the conflicting reports may be due, on theoretical grounds at least, to the almost universal failure to take into consideration possible variations in plasma viscosity. Indeed, recent studies^{1,2} suggest that this factor alone

may be of importance in influencing the level of arterial blood pressure. Certainly, variations in blood viscosity, in the presence of identical hematocrit values, may be dependent upon differences in plasma viscosity. On this basis, the observation, by Harris and McLaughlin,³ of increased blood viscosity in 35 of 40 hypertensive individuals with normal hematocrit values might be interpreted as being dependent upon increased plasma viscosity.

The present study was undertaken for the purpose of investigating the viscosity of the blood plasma in essential hypertension and its relation to certain factors that may influence it. By far the most important of these are the plasma proteins; it is, indeed, questionable whether any other factor is of practical significance in this connection under conditions compatible with life. Plasma lipid determinations were made because of the theoretically possible effect of these substances upon viscosity, as suggested by Fishberg.⁴

Material and Methods. Determinations were made upon 23 samples of blood obtained in the postabsorptive period from 21 patients with essential hypertension, with and without evidence of renal functional impairment. In addition, similar studies were made in 9 normal individuals and in 7 other patients for purposes of comparison. Heparinized plasma was employed for the viscosity and protein determinations and oxalate plasma for the lipid estimations. Plasma viscosity was measured by a concentric cylinder method¹ with the substitution of a more delicate torsion wire in order to increase the sensitivity of the apparatus for use with plasma. All viscosity values are recorded as relative to water at 37° C. The plasma protein fractions were separated by the method of Howe,⁵ employing appropriate concentrations of sodium sulphate, buffered according to the suggestion of Medes;⁶ fibrinogen and globulin were determined by difference. Digestion was accomplished by phosphoric-sulphuric acid mixture and potassium persulphate,⁷ and the nitrogen was determined by distillation and titration. All determinations were performed in duplicate. Fatty acids were determined by the oxidation method of Bloor,⁸ cholesterol by the method of Myers and Wardell⁹ and lipid phosphorus by the method of Youngburg.¹⁰

Observations and Discussion. The values for the various plasma protein fractions and plasma viscosity in 9 normal individuals are presented in Table 1. The protein values are in close agreement with those reported by other investigators^{11,12} who employed the same methods. The viscosity values for normal heparinized plasma, ranging from 1.76 to 1.99, averaging 1.88, are somewhat higher than those previously reported for oxalate plasma.¹

The data obtained in the group of 21 patients with essential hypertension are presented in detail in Table 2. The total protein concentration, ranging from 5.61 to 8.66 gm. per 100 cc., shows a distinct tendency to vary within the high normal range, the average

of 7.45 being raised to 7.54% if the last case (D. Mc.), with a rather advanced grade of renal functional insufficiency, be excluded from the calculation. Govaerts¹³ believed that the plasma protein concentration, as well as the osmotic pressure per gram of protein, was increased in essential and in nephritic hypertension. On the other hand, Moore and Van Slyke¹⁴ could demonstrate no consistent relationship between the concentration of plasma proteins and the degree of elevation of blood pressure in patients with nephritis. The plasma globulin values in this series are within the normal range, but those for fibrinogen (0.16 to 1.18, averaging 0.5 gm. per 100 cc.) and, in consequence, those for globulin plus fibrinogen (2.19 to 4.19, averaging 3.37 gm. per 100 cc.), are distinctly above normal. Fibrinogen values above 0.4 gm. were obtained in 11 of the 23 determinations in this group.

TABLE 1.—NORMAL INDIVIDUALS.

Case.	Viscosity.	Fibrinogen.	Globulin.	Fibr. + globulin.	Albumin.	Total protein.	NPN., mg. %
		Grams per 100 cc.					
♂ T. H.	1.90	0.29	2.28	2.57	4.61	7.18	28
♂ W. L.	1.76	0.21	2.24	2.45	4.45	6.90	30
♂ F. R.	1.89	0.26	2.49	2.75	4.62	7.38	29
♂ W. S.	1.88	0.28	2.99	3.27	3.61	6.88	32
♀ A. C.	1.88	0.16	3.42	3.58	3.45	7.03	31
♀ A. N.	1.82	0.22	3.01	3.23	4.60	7.83	29
♀ L. L.	1.94	0.17	2.44	2.61	4.80	7.41	32
♀ R. H.	1.99	0.32	2.77	3.09	4.22	7.31	21
♀ M. Y.	1.85	0.18	2.68	2.86	4.39	7.25	19
Average	1.88	0.23	2.70	2.93	4.31	7.24	

The plasma viscosity values in the patients with essential hypertension range from 1.84 to 2.27 and the average, 2.01, is distinctly higher than the normal average (1.88). In only 1 instance (T. F., Table 2) was the viscosity below the average normal; a subsequent determination (11 weeks later) yielded a much higher figure. However, 10 values in this group are below the high normal figure (1.99), 13 being above the upper limit of normal. In view of these observations it would appear that previously reported high blood viscosity figures in hypertensive patients with normal hematocrit values may be due to increased plasma viscosity.

No attempt will be made here to review the literature dealing with the relationship between proteins and the viscosity of the plasma and serum; this has been done elsewhere.¹⁵ The present data, as presented in Fig. 1, in which plasma viscosity is plotted against total plasma protein concentration, indicate that in normal

as well as abnormal plasma there is no consistently close relationship between these two factors. This is to be expected, since plasma, normal and abnormal, contains an undetermined number of protein fractions of variable concentration, each probably influencing the viscosity to a different degree. Unfortunately, despite the enormous amount of data available regarding the viscosity of several proteins under a variety of conditions, absolute values are not available for each of the plasma protein fractions under conditions prevailing in the plasma. However, it is generally recognized that fibrinogen has the highest and albumin the lowest vis-

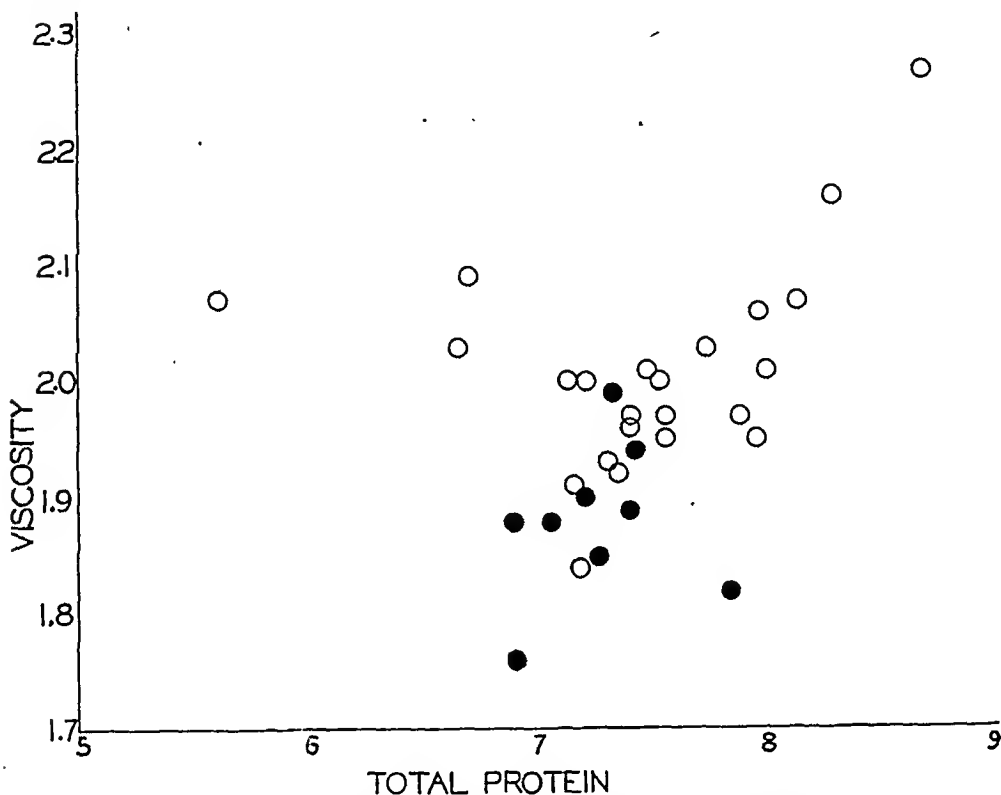


FIG. 1.—Viscosity plotted against total plasma protein. Open circles, cases of essential hypertension; solid circles, normal individuals.

cosity, the several globulin fractions occupying positions intermediate and transitional between these two.¹⁶ As may be noted in Table 2, in many cases in the present series increased viscosity was associated with an increased fibrinogen or "globulin + fibrinogen" concentration; however, in a few instances, relatively low viscosity was associated with a high fibrinogen content, and *vice versa*.

The greatest divergence between plasma viscosity and total protein concentration occurs in those instances in which the albumin fraction is low. Since the effect of this protein upon plasma viscosity is relatively slight, normal values for the latter may be

obtained in spite of marked diminution in the former; indeed, in the presence of a simultaneous increase in globulins or fibrinogen, or both, as frequently happens, the plasma viscosity may be quite high. This is well illustrated in Case R. J., Table 3. This case, as well as others in this series, also indicates the apparent lack of influence of plasma lipids upon plasma viscosity. Fishberg⁴ believed that an increased cholesterol content tends to diminish viscosity by favoring a water-in-oil type of emulsion. The fatty acids were slightly above normal in many cases in the hypertensive group, the average concentration, 465 mg. per 100 cc., being considerably higher than the average value, 353 mg., obtained by Boyd¹⁷ in normal individuals. This factor, however, bore no demonstrable relation to the plasma viscosity, as indicated by Case M. M., in Table 3, with an extremely high fatty acid concentration and relatively low viscosity, in spite of a rather high fibrinogen content. We believe that, under conditions ordinarily existing in the blood, the plasma viscosity is practically unaffected by changes in factors other than the plasma proteins, particularly fibrinogen and globulin. In our opinion, the discrepancies which apparently exist between viscosity and protein concentrations would be eliminated if the individual viscosities and concentrations of the several globulin fractions were known.

There was no consistent relationship between plasma viscosity and either systolic or diastolic blood pressure in the present series. Two normal cases presented higher viscosity values than several in the hypertensive group; moreover, an increased viscosity may accompany acute infectious processes with an associated increase in plasma fibrinogen and, at times, globulin, as in Case E. R., Table 3, with no rise in blood pressure. It would appear unlikely, therefore, that increased plasma viscosity is of fundamental importance in the pathogenesis of hypertension. However, it may be possible that vascular hypertension is in part dependent upon changes incident to the effects of increased plasma viscosity persisting over long periods of time.

Summary. 1. The total plasma protein concentration in a group of 21 patients with essential hypertension was within practically normal limits, the average being somewhat higher than the average normal. The albumin and globulin fractions were approximately normal but the fibrinogen concentration was considerably elevated in a large proportion of patients in this series.

2. The plasma viscosity was generally higher in essential hypertension than in normal individuals but values below the upper limit of normal were present in some instances. There was no demonstrable relationship between the plasma viscosity and the degree of hypertension.

3. The concentration of fatty acids was slightly above normal and the average considerably above the average normal. The plasma lipids appeared to bear no relation to the plasma viscosity.

TABLE 2.—ESSENTIAL HYPERTENSION.

Case.	Age.	Plasma proteins.				Plasma lipids.			Urea clear., %.	Hb., %.	R.B.C., millions.	Urine.			Eye-grounds.	Blood pressure.		
		Fib.	Glob.	Fib. + glob.	Alb.	Total prot.	Choles. terol.	NPN.				Alb.	Casts.	Sp. gr.				
								Fatty acid.									Lipoid P.	
																		Mg. per 100 cc.
J. B. ♂	40	1.97	2.44	3.70	4.17	7.87	147	468	7.1	28	153	92	4.75	1.028	0	0	1.028	195/120
A. W. ♀	50	2.03	2.33	2.60	4.04	6.61	159	412	7.3	37	105	78	4.05	1.034	0	0	1.034	200/140
A. N. ♀	55	1.97	3.37	3.05	4.34	7.39	160	462	8.2	29	98	85	4.00	1.020	0	0	1.020	220/120
C. T. ♀	40	2.07	3.37	4.02	4.09	8.11	160	462	8.2	32	84	90	4.60	1.035	0	0	1.035	180/110
*W. J. ♂	53	2.27	3.26	3.68	4.59	8.27	256	524	6.8	40	78	100	5.30	1.016	+	+	1.016	220/140
M. S. ♀	54	1.91	3.32	4.19	4.47	8.66	293	586	7.1	49	73	90	5.25	1.022	+	+	1.022	180/100
B. B. ♂	45	1.95	2.88	3.27	3.87	7.14	235	425	6.9	32	68	88	4.60	1.026	0	0	1.026	190/110
B. L. ♀	55	1.96	3.01	3.40	4.14	7.54	186	472	6.8	25	68	90	4.90	1.026	0	0	1.026	206/100
J. C. ♀	44	2.01	2.72	2.96	4.42	7.38	183	427	8.7	25	66	83	4.20	1.016	0	0	1.016	190/110
E. G. ♀	48	2.06	3.31	4.08	3.81	7.89	140	490	7.6	26	66	86	4.10	1.024	0	0	1.024	200/110
L. W. ♂	66	2.03	3.01	3.34	4.38	7.72	176	442	6.4	29	62	88	4.60	1.020	0	0	1.020	210/110
M. D. ♂	27	1.93	3.01	3.58	4.36	7.94	113	432	6.7	25	61	67	3.50	1.030	0	0	1.030	185/120
H. W. ♂	64	2.00	2.19	2.85	4.44	7.29	210	465	7.2	37	55	80	4.10	1.021	0	0	1.021	190/110
F. Y. ♀	40	1.93	2.67	3.85	3.67	7.52	206	426	9.1	30	54	92	4.10	1.022	0	0	1.022	180/115
M. P. ♀	34	2.01	2.44	2.71	4.76	7.47	180	416	7.4	30	53	82	4.20	1.030	0	0	1.030	185/115
J. Mc. ♀	53	1.97	2.71	3.09	4.45	7.54	253	570	7.8	27	48	85	4.10	1.020	0	0	1.020	210/120
S. W. ♀	39	2.09	2.72	2.90	3.78	6.68	138	432	6.4	21	40	77	5.50	1.021	0	0	1.021	200/120
T. F. ♂	63	1.84	2.75	3.03	4.14	7.17	138	432	6.4	41	39	95	4.10	1.020	0	0	1.020	220/120
L. P. ♀	51	2.00	2.66	2.98	4.21	7.19	184	432	6.4	30	32	100	5.10	1.022	0	0	1.022	170/100
A. C. ♀	33	2.00	2.69	3.10	4.24	7.34	286	570	7.8	38	31	94	5.10	1.012	+	+	1.012	220/105
D. Mc. ♂	50	2.07	2.69	3.71	3.40	7.11	158	432	6.4	47	22	72	3.60	1.024	+	+	1.024	170/115
Average	..	2.01	0.50	2.84	3.37	7.45									0			

* (1) March 13, 1935. (2) April 30, 1935.

† (1) March 6, 1935. (2) May 28, 1935.

TABLE 3.—Miscellaneous Conditions.

Case.	Age.	Condition.	Viscosity.	Plasma proteins.			Plasma lipids.			NPN.	Urea clear., %.	Hb., %.	R.B.C., millions.	Blood pressure.		
				Fib.	Glob.	Fib. + glob.	Alb.	Total prot.	Chol. esterol.						Fatty acid.	Lipoid P.
Grams per 100 cc.										Mg. per 100 cc.						
M. M.	18	Subsiding, acute	1.90	0.67	2.47	3.14	1.68	4.82	726	1264	12.8	39	29	80	4.3	140/100
F. T.	33	Chronic nephritis	1.77	0.14	2.61	2.75	3.36	6.11	46	48	50	3.0	170/110
G. P.	23	Chronic nephritis	1.75	0.11	2.23	2.34	4.23	6.57	27	68	87	4.5	170/120
R. J.	31	Lipoid nephrosis	2.13	0.61	2.69	3.30	1.07	6.42	642	1014	9.3	24	88	74	4.2	116/92
T. S.	34	Convalescent toxemia of preg	1.96	0.17	2.86	3.03	1.76	4.79	248	22	..	74	4.1	150/90
F. R.	32	Acute gonococcus arthritis	2.20	0.67	3.56	4.18	3.50	7.68	31	..	88	4.8	120/90
J. F.	47	Prostatism	1.91	3.29	3.98	7.27	110	..	68	3.7	136/74

4. The relationship between the various plasma proteins and plasma viscosity may perhaps be more clearly established when the concentrations and relative viscosities of the several globulin fractions can be determined accurately.

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THE USE OF CALCIUM GLUCONATE AS A CIRCULATION TIME TEST.*†

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THE need of more satisfactory objective methods of estimating cardiac function is too obvious to require comment. Exercise tolerance tests and vital capacity determinations are of limited

* Calglucon, 20%, used in this study, was made available through the courtesy of the Sandoz Chemical Works, Inc.

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usefulness, and venous pressure measurements afford no direct information as to the state of the pulmonary circulation.

The volume of blood pumped by the heart each minute is conveniently spoken of as the "cardiac output," and is for practical purposes the most satisfactory criterion of its functional efficiency. Determination of the cardiac output, however, is difficult, and only recently have methods been developed which give accurate results.¹ The velocity of the blood flow, however, may easily be determined with a fair degree of accuracy, and represents in considerable measure the effect of cardiac work and cardiac strain.

Many methods have been proposed for estimating the speed of the circulation, the majority of which depends upon the injection of a foreign substance into the circulation at one point and detecting its arrival at another by means of a signal or end reaction. The term "circulation time" denotes the interval of time necessary for

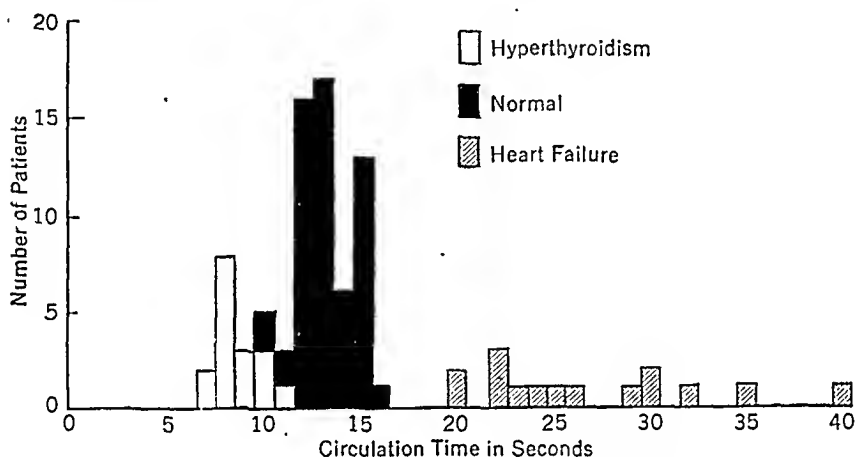


CHART 1.—CHART OF CIRCULATION TIMES IN DIFFERENT CONDITIONS.

the fastest particle of a foreign substance to traverse the shortest available path between the point of injection and the place of detection.² Thus, the interval elapsing from the moment of injection of a bitter substance into an antecubital vein and its perception on arrival in the tongue is spoken of as the "arm to tongue circulation time," and necessarily includes the blood flow through the lungs, which is the major portion of the path.

Robb and Weiss³ and Blungart and Yens⁴ have each proposed criteria which should be met by the ideal procedure for determining circulation time. The substance must be non-toxic in the amounts utilized; it should itself not affect the rate of blood flow; the reaction time after arrival in the end organ should be short, and the signal should be clearcut; the effect should wear off quickly to allow of repeated measurements; and finally, it should be objective and, if possible, suitable for graphic registration.

Methods. Since the early experiments with fluorescein by Koch,⁵ the following substances have at one time or another been employed

in determining the speed of the circulation. An active radium deposit;^{4, 6} histamin phosphate;⁷ sodium dehydrocholate;⁸ sodium cyanid;^{3, 9} saccharin;¹⁰ endoiodin, an organic iodine preparation;¹¹ calcium chlorid and calcium bromid;¹² volatile substances such as ether and perfumes for measuring the velocity on the arterial side of the pulmonary bed.¹³

Technical difficulties, expense, untoward or toxic effects, and the possibilities of venous thrombosis and local tissue damage are some of the objections that have at times been recognized in one or another procedure, in some instances by the proponent of the method himself.

Technique of Calcium Gluconate Test. A satisfactory method should be capable of being utilized by the practitioner at the bedside, employing the resources ordinarily at his command. The material should be readily available, free from toxic effect, and incapable of causing pain, thrombosis or tissue necrosis when rapidly injected. Such criteria are met by calcium gluconate, which in this country has become the preparation usually employed when intravenous or intramuscular calcium medication is indicated. The patient reclines, with the arm at the level of the right auricle. After entering the vein, the tourniquet is withdrawn, and the circulation is permitted to return to normal. A stopwatch is held in the left hand, and 3 to 5 cc. of the 10% solution is injected as rapidly as possible with the other, through an 18-gauge needle. When the larger amount is used, a characteristic response is invariably elicited. The time required for completing the injection is subtracted from the total circulation time, although if a needle of large bore be used, this rarely occupies more than $\frac{1}{2}$ second. There has been recently made available a 20% solution of calcium gluconate which permits the use of smaller volumes, and minimizes the factor of injection time. Recent tests have been carried out with 2.5 cc. of this solution with improved results. There is no pain, thrombosis or slough should the injection be improperly made. The patient announces the onset of the hot sensation in the pharynx by crying out "hot," or some other such signal. The sensation is sudden in onset, and wells up rapidly into the throat very much like a "gust of steam," to use the expression of one patient. It is next felt in the face, and then successively in the anterior chest, perineum, the hands, and finally the feet. These effects depend upon the arrival of the solution in the respective peripheral arterial beds. The onset of the sensation in the throat and tongue is most intense, as the substance is here present in greatest concentration.

After the sensation has entirely subsided, usually within 1 or 2 minutes, the reading may be repeated, without removing the needle from the vein. The second reading usually checks closely with the first, indicating that the first injection of the material has no great effect on the circulation itself. No discomfort is experienced by

the patient as a result of the rapid injection, even in those with advanced heart failure. One patient with auricular fibrillation and severe heart failure of rheumatic origin complained of palpitation shortly after the test, but this was the only instance observed. We have tested a number of patients who were under digitalis medication and have observed no instance of untoward calcium and digitalis synergism. This method has the additional advantage that circulation time readings to the extremities may be made, if desired, affording a possible approach to the study of peripheral vascular disease. However, it is entirely subjective and cannot be carried out without the coöperation of the patient.

Most of our patients were at rest in bed in the hospital, some were dispensary patients, and others were seen at home or in the office. We have not found it necessary to perform the test under basal conditions, as advocated by some, inasmuch as Boothby and Rynearson¹⁴ have shown that the increase in cardiac output in hyperthyroidism is greater than that observed when the metabolism of normal subjects is raised to a corresponding level by exercise. They conclude that there is an additional factor in hyperthyroidism which stimulates the circulation beyond that required by the metabolic demands of the tissues. Furthermore, Rosenblum states that when the level of metabolism is raised by dinitrophenol,¹⁵ the circulation speed is not increased as it is with the administration of thyroid substance or in spontaneous hyperthyroidism.

Results. Duplicate readings were made on 156 patients. In those with cardiac failure, as many as 6 or 8 duplicate tests were made at various times during their illness, and recovery of compensation was always associated with a shortening in circulation time. The results are shown in Table 1.

TABLE 1.—CIRCULATION TIME DETERMINATION IN 156 PATIENTS.

Condition.	No. of patients.	Reading in seconds.			Probable error.
		Lowest.	Highest.	Mean.	
Normal	60	10	16	12.5	±1.0
Hyperthyroidism	17	7	11	9.9	±1.1
Cardiac failure	15	20	40	26.7	±3.8
Myocardial insufficiency	11	16	23	18.7	
Bronchial asthma	4	12	14	13.0	
Nephritis with and without edema	2	13	13	13.0	
Compensated valvular heart disease	8	11	14	13.0	
Hypertension	25	8	16	12.0	±1.4
Fever	7	8	13	10.0	
Anemia	3	8	11	9.0	
Myxedema and hypothyroidism	4	19	22	20.0	

The group of 11 patients designated "myocardial insufficiency" were not decompensated, but in several there had been previous episodes of coronary thrombosis, and all showed electrocardiographic evidence of myocardial disease. There were no com-

plaints, except fatigue and dyspnea on exertion, and no physical signs of heart failure. One patient, in a severe attack of bronchial asthma, had a normal circulation time of 14 seconds. A woman with general anasarca caused by nephritis, showed a reading of 13 seconds. There were 8 patients with healed, compensated rheumatic valvular lesions who showed normal readings. Likewise, 25 patients with uncomplicated hypertension had circulation times from 8 to 16 seconds (average, 12).

In 21 patients, before or immediately after the tests with calcium gluconate, we carried out duplicate determinations with decholin. In these there was complete correspondence in 7 patients, a difference of less than 1 second in 9; less than 2 seconds in 1; less than 3 in 2, and a variation of 4 to 6 seconds in 2 other patients.

Summary and Conclusions. The arm to tongue circulation time, a relative index of the rate of blood flow through the lungs, is a useful test of the functional efficiency of the circulation. The velocity with which the blood flows through the lungs is a composite result of the oxygen demands of the body and the capacity of the heart and bloodvessels to propel the blood to meet such demands.

A simple method is described which lends itself to general use, and the results in 156 normal and pathologic cases are reported. The calcium gluconate method gives normal readings varying from 10 to 16 seconds, with an average arm to tongue circulation time of 12.5 seconds.

Hyperthyroidism increases the velocity of the blood flow, and cardiac failure markedly slows it. In myxedema and hypothyroidism there is a slowing of the circulation in proportion to the fall in metabolism. The test is helpful in the differentiation of edema of cardiac or renal origin, and may be of assistance in distinguishing between cardiac and bronchial asthma. The calcium gluconate test is approximately accurate, and easy to perform. No untoward effects have been observed, nor has there been any thrombosis or tissue damage in a single instance.

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THE EFFECT OF TWO WATER-INSOLUBLE SQUILL GLUCOSIDS UPON THE ELECTROCARDIOGRAM.

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SINCE the days of Withering¹ and his brilliant research upon foxglove in the treatment of dropsy, digitalis has overshadowed all the other drugs of this group in the treatment of cardiac edema. Squill, while consistently used for similar purposes, has occupied a position of secondary importance. The use of squill in medicine

dates back many centuries. Scheer and Sigerist,² in writing the history of squill, mention that Pythagoras and Galen recommended it to "prolong life," and describe its use by the early Egyptians and also the Romans.

The recognition that the members of this family of drugs are each composed of a number of glucosids has led to an immense amount of research for the purified glucosidal elements of both digitalis and squill. The processes for isolation and analysis of insoluble glucosids of squill were perfected by Dyas³ and Ingersoll.⁴

Van Dyke and Wallace⁵ investigated two of these squill glucosids in animals (scillonin A and B) and found they were less cumulative than ouabain, although the acute toxic effects produced by continuous intravenous injection were the same. Carr and Mayer⁶ have recently reported favorable clinical experience with scillonin. They found that cardiac irregularity was a sign of intoxication as it is in digitalis. The Council on Pharmacy and Chemistry accepted the material last year.⁷

We have made a further evaluation of the cardioactivity of these glucosids in heart disease with congestive heart failure with electrocardiographic studies. Many serial electrocardiograms were taken on our patients before, during and after squill medication, giving a mobile picture of the effects of squill upon the electrocardiogram. With the renewal of interest in squill derivatives in the past few years we felt it worth while to report our findings of the electrocardiographic changes caused by this drug.

The effect of squill and its glucosids upon the electrocardiogram has not received a great deal of attention. In 1911, Turnbull⁸ recorded the production of sinus arrhythmia, heart block, and "an irregularity whose nature cannot be decided with certainty but which may be a condition of heart alternation, or may be due to extrasystoles." One electrocardiogram taken in this study showed prolongation of the *P-R* interval from 0.16 to 0.3 second, and dropped ventricular beats.

In 1911, Windle⁹ recorded partial and complete heart block in a patient as a result of digitalis, squill and strophanthus.

White, Balboni and Viko¹⁰ (1920) reported on the "digitalis-like action of squill." They found that heart block was produced only by large doses of squill and that the *T* waves were flattened or inverted.

Kauffman¹¹ (1923) reported a series of cases of auricular fibrillation treated with digitalis and quinidin and squill and quinidin. He recorded the percentage of conversion to sinus mechanism as 41.3% with quinidin combined with digitalis. When squill and quinidin were used together he secured a higher percentage of 61.1%.

Boden and Neukirch¹² (1923) reported a patient with auricular flutter who regained a sinus mechanism under the influence of squill and relapsed to auricular flutter when the squill was discon-

tinued. They reported the electrocardiograms of warm-blooded animals showed extrasystoles, auriculoventricular block and ventricular standstill with continued beating of the auricles under the influence of squill.

Estabe¹³ (1928) reported a patient with valvular disease in whom digitalis produced an auriculoventricular block. He changed the medication to squill because of its supposed non-cumulative action. Auriculoventricular block again resulted similar to that produced by the digitalis.

Van Dyke⁵ (1933), in his studies of seillonin in cats and dogs, recorded an increased *P-R* interval, dropped beats, sinoauricular block and ventricular extrasystoles.

The effect of digitalis on the electrocardiogram has been more intensively studied with varied reports. The first records are credited to Cohn¹⁴ and his coworkers in 1915. They reported the effects upon the *R-T*, *S-T* segments and *T* waves as present in 30 of 34 cases studied. They noted that the effect of the drug lasted in some cases as long as 22 days. Cohn mentioned several investigators who reported the effect of digitalis upon the electrocardiograms of animals in which the heights of the *T* waves were increased.

Pardee¹⁵ (1924), in studying the rate of absorption of digitalis from the gastro-intestinal tract, reported: "The action of the heart muscle, as shown by the change in the *T* wave, begins between 2 to 4 hours after a dose of 1 minim of the tincture for each pound of weight . . . diminution in its height, or a sinking of the level before the *T* . . . which later results in an inversion of the *T* in one or more leads."

Pardee¹⁶ (1923) in studying standardization methods of digitalis by its action on the human heart, stated: "This change in the *T* wave of the electrocardiogram comes on after small amounts of digitalis have been given by mouth, and increases steadily in degree as more of the drug is given."

Pardee,¹⁷ in his book, states: "The effect of digitalis is very characteristic and usually consists of a diminution of the height of the *T* with a depression . . . when right or left axis deviation is present the effect of the digitalis changes the *T* wave in such a way that it finally comes to be opposite in each lead to the direction of the predominant waves of the *Q-R-S*."

Brams¹⁸ (1931) stated: "Electrocardiograms taken at frequent intervals over a long period of time failed to show a constantly lowered *T* wave. The *T* wave was never seen to be negative."

Coelho,¹⁹ in studies on dog and human electrocardiograms, found only 18% showed changes in the *T* wave, disagreeing with American investigators.

A few reports of the clinical and electrocardiographic studies of squill, and the more comprehensive studies made with digitalis, would imply that the effects of the two drugs are somewhat the

same. The results of our studies with urginin* are in accord with these findings.

Method of Study. Twenty-five consecutive cases of heart disease with edema in the heart ward at the Cook County Infirmary were selected for study of the cardioactivity of urginin. The clinical diagnosis of these patients is appended in Table 1. All cases were in serious congestive heart failure with gross edema, with a functional classification of Group III, according to the standards of the American Heart Association.²⁰

A number of these cases were of the coronary and syphilitic types of heart disease, where digitalis or squill may not have been the medication of choice. The patients were selected consecutively, however, on the basis of edema which did not recede with bed rest during the observation period.

Each case was carried through a control period of 5 to 20 days until evidence was established that bed rest was not effective in reduction of the edema. Electrocardiograms taken on alternate days during this period of observation gave evidence that there was no digitalis effect in the electrocardiograms. Only 3 cases, however, had received the drug within the 4 weeks prior to the observation period.

During the period of study of 5 to 20 days, the only medication given was liquid petrolatum, morphin sulphate and urginin. Fluid intake was not limited nor was salt restricted from the diet. Electrocardiograms with the conventional three leads were taken on alternate days and chest leads every fourth day. The patients were weighed daily at 7 A.M., their 24-hour daily fluid intake and urinary output were recorded and graphed. Apical and radial pulse rates were counted for 60-second periods at 8 A.M., 12 noon, 4 P.M. and 8 P.M. and graphed.

A period of observation following the medication was made upon the majority of the patients and 5 cases were restudied with digitalis for comparison.

Dosage. Urginin was administered in tablet form once, twice or thrice daily after meals. Each tablet contained 0.5 mg. of the purified glucosid. The method of dosage varied in each individual, depending upon his response to the drug. Some patients received 3 mg., 6 tablets per day, for the first 2 to 4 days, followed by a reduction to 0.5 to 1.5 mg. for maintenance dosage. In others the original dosage was only 2 mg. with reduction to maintenance dosage later. A few patients were given daily doses of 1 to 1.5 mg. daily over a period of 10 to 40 days.

Results. Ventricular Rate. The ventricular rate was decreased in 21 of the 25 patients (84%). The decrease occurred in the patients with a normal sinus mechanism or auricular fibrillation. The 4 exceptions included 1 patient with chronic auricular flutter, 2 with uremia to which they succumbed, and 1 with a bronchopneumonia which caused his death. The decrease in the ventricular rate was most obvious in the group with auricular fibrillation and least marked in those with syphilitic heart disease.

Nineteen patients had a sinus mechanism, to whom urginin was administered from 7 to 32 days, with an average daily dose ranging from 1.3 to 2.22 mg.

* A mixture of equal parts scillonin A and scillonin B (Grisard-Dyas) accepted under the name "urginin" by the Council of Pharmacy and Chemistry of the American Medical Association.

TABLE 1.—CARDIAC DIAGNOSES.

Case No.	Etiologic	Anatomic	Physiologic
1	Thyrototoxicosis Thymoma	Occlusion of the superior vena cava Cardiac dilatation	Sinus mechanism.
2	Hypertension	Cardiac hypertrophy Coronary sclerosis	Sinus mechanism.
3	Hypertension Arteriosclerosis Uremia	Cardiac hypertrophy Coronary sclerosis	Sinus mechanism.
4	Arteriosclerosis	Myocardial fibrosis	Auricular fibrillation.
5	Arteriosclerosis	Coronary thrombosis Myocardial infarction	Sinus mechanism. Extrasystoles (ventricular)
6	Syphilis	Cardiac hypertrophy Aortic regurgitation Aortitis with dilatation	Prolonged P-R interval. Sinus mechanism.
7	Hypertension Arteriosclerosis	Cardiac hypertrophy Coronary thrombosis (old) Coronary sclerosis	Sinus mechanism.
8	Hypertension	Cardiac hypertrophy Coronary sclerosis	Sinus mechanism. Extrasystoles (ventricular)
9	Pulmonary disease	Cor pulmonale	Sinus mechanism. Extrasystoles (ventricular)
10	Hypertension Arteriosclerosis	Cardiac hypertrophy	Sinus mechanism. Auricular flutter. Auricular fibrillation.
11	Thyrototoxicosis	No cardiac disease	Sinus mechanism.
12	Syphilis	Aortitis with dilatation	Sinus mechanism.
13	Syphilis	Cardiac hypertrophy	Sinus mechanism.
14	Hypertension Arteriosclerosis	Aortitis Cardiac hypertrophy Coronary sclerosis	Auricular fibrillation. Sinus mechanism. Extrasystoles (ventricular)
15	Hypertension	Cardiac hypertrophy	Sinus mechanism.
16	Hypertension Arteriosclerosis	Cardiac hypertrophy Coronary sclerosis	Sinus mechanism.
17	Hypertension Arteriosclerosis	Cardiac hypertrophy Coronary sclerosis Coronary thrombosis	Complete A-V dissociation.
18	Hypertension Arteriosclerosis	Cardiac hypertrophy	Auricular fibrillation.
19	Hypertension	Cardiac hypertrophy	Auricular fibrillation.
20	Arteriosclerosis Hypertension	Coronary sclerosis Coronary thrombosis Cardiac hypertrophy	Left bundle-branch block with prolonged conduction time; A-V block.
21	Hypertension Arteriosclerosis	Coronary sclerosis Coronary thrombosis Cardiac hypertrophy	Left bundle-branch block. Partial auriculoventricular block.
22	Chronic bronchiectasis Chronic emphysema	Cor pulmonale	Sinus mechanism.
23	Arteriosclerosis Hypertension	Cardiac hypertrophy	Sinus mechanism.
24	Hypertension	Cardiac hypertrophy	Auricular fibrillation.
25	Arteriosclerosis Diabetes mellitus Hypertension	Coronary sclerosis Myocardial fibrosis	Sinus mechanism.

P Waves. No conclusions could be drawn concerning the effect upon the *P* waves. We found that the contour of the *P* waves varied mildly in the control studies. During the control and medication period, it was not uncommon to find slight changes in the contour of the auricular complexes, such as change in height, notch-

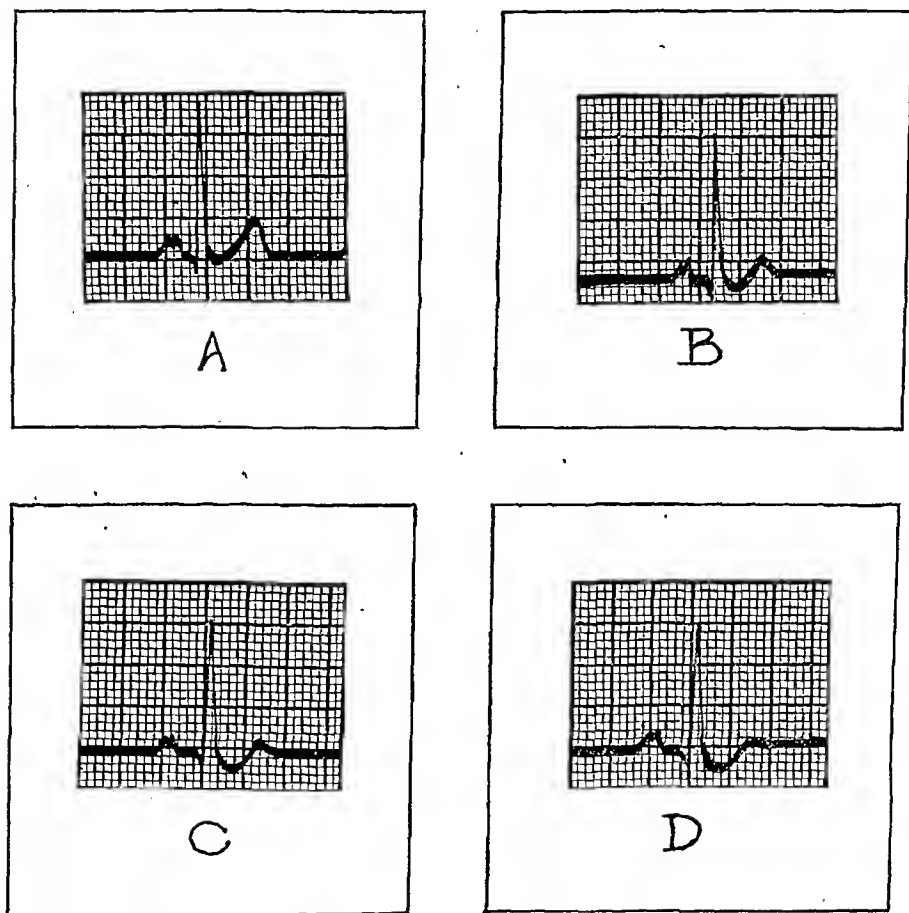


FIG. 1.—A, Control before medication. B, Slight depression of *R-T* segment and lowered *T* wave (5 days). C, Further depression of the *R-T* segment and lowered *T* wave (10 days). D, Concavity of *R-T* segment and almost total obliteration of *T* wave (15 days). Lead I throughout.

ing and widening. These changes were not sufficiently consistent, however, to warrant description of definite changes due to drug effect.

Effects Upon the P-R Interval. The *P-R* interval was prolonged in 16 of the 19 cases. Of the 3 patients whose electrocardiogram showed no change in the *P-R* interval, one received 23.5 mg. of urginin over a period of 18 days with an average dose of 1.3 mg.

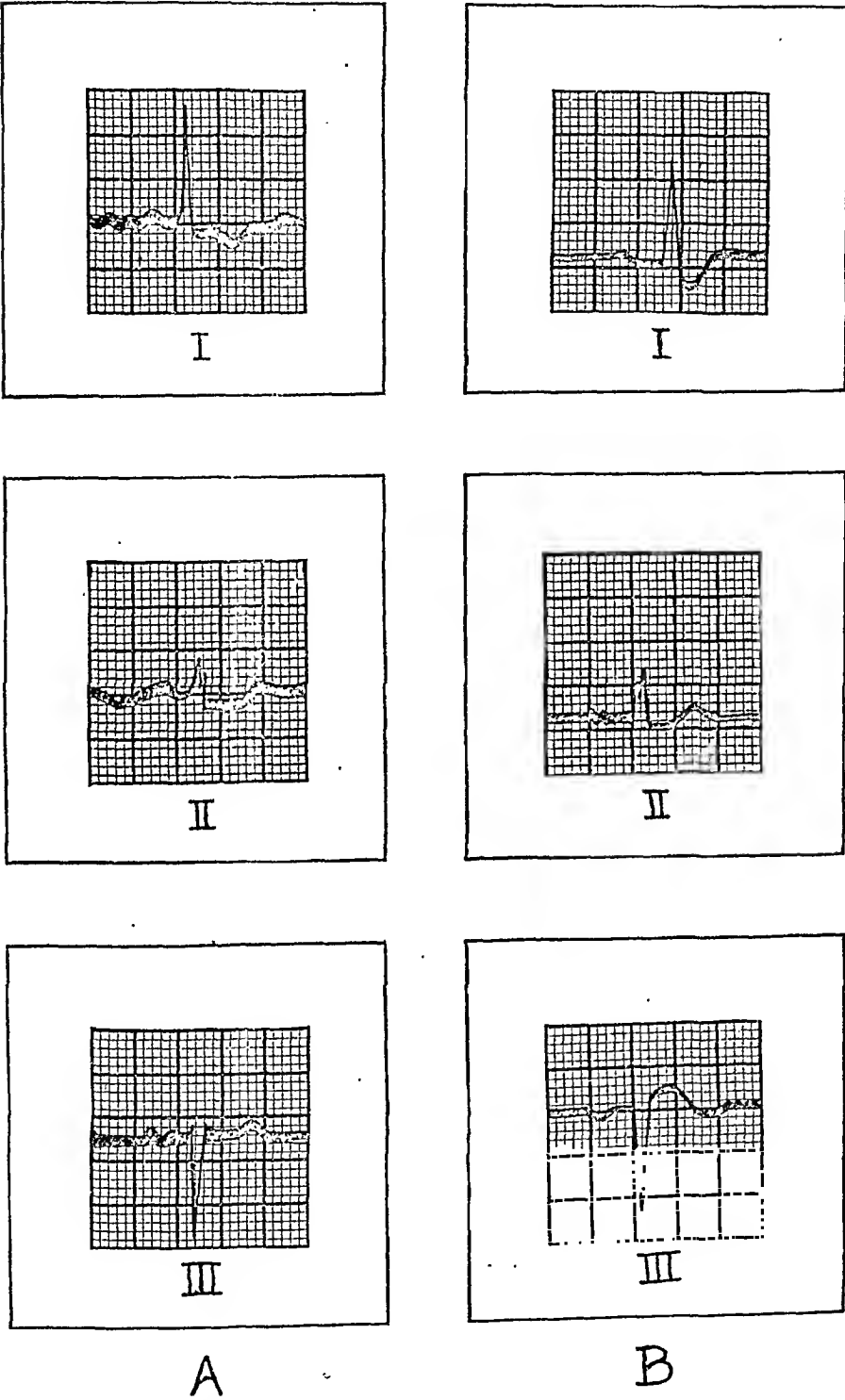


FIG. 2.—A, Electrocardiogram with left axis deviation before medication. B, Electrocardiogram with left axis deviation after 20 days of medication. (Total uroginin intake, 30 mg.)

of urginin per day. The second received 61 mg. of urginin over a period of 32 days with an average daily dose of 2.21 mg. This patient was later checked with digitalis, receiving 51 grains of a known potent product over a period of 17 days with an average daily dose of 3 grains, without demonstrable change in a $P-R$ interval of 0.2 second. All 3 of these patients showed characteristic changes in the $R-T$ and $S-T$ segments. Two were hypertensive vascular problems and 1 a case of syphilitic aortitis.

The minimal change recorded in the $P-R$ interval was 0.02 second and the maximum increase was 0.12 (control, 0.16; medication period, 0.28). Prolongation of the $P-R$ interval was not proportionate to the amount of drug administered. The patient who showed the maximum change of 0.12 second received only 14 mg. over a period of 7 days, or 2 mg. per day. Similar or greater dosage in other patients showed a lesser change.

Effect Upon the Q-R-S Complexes. No consistent changes were noted in the time interval of the $Q-R-S$ complexes. The height sometimes varied but this appeared to be consistent with increase or decrease of edema. The descending limb of the R spike projected below the base line as described in the next paragraph with changes in the $R-T$ segment. Similarly the ascending limb of the S wave in Lead III projected above the base line as the $S-T$ segment was changed.

One series of electrocardiograms showed a prominent Q wave in Lead III, which became shorter under medication and longer after the drug was discontinued.

Effect Upon the R-T and S-T Segments. The $R-T$ or $S-T$ segment was affected in all 25 cases. With a dosage of 1 to 3 mg. per day, this change was usually noted on the fourth or fifth day of medication. In those cases with the $Q-R-S$ complex directed upward in all leads, the isoelectric $R-T$ segment became concave, with mild blunting of the peak of the T wave when it was directed upward. With continued administration of the drug, the concavity deepened and the descending limb of the R spike progressed below the base line, while the T wave became obliterated. These changes were present in all leads, usually most marked in Leads II and III.

In those cases with diphasic or inverted T waves the $R-T$ segment was sometimes directed diagonally or showed a convex curve. The effect of urginin on these segments was similar in that they assumed the same concave appearance as that described above, although the descent of the descending limb of the R wave below the isoelectric level was less marked.

In cases with left axis deviation with the T wave directed upward in Lead III, the change in the $S-T$ segment consisted of a convexity with deformity of the T wave. The ascending limb of the S spike progressed above the base line.

T-wave Effects. The contour of the T wave was affected in all

cases but this appeared to be a part of the change in the $R-T$ or $S-T$ segment. No case showed straight inversion of the T waves in any lead.

Auricular Fibrillation. Four cases of auricular fibrillation were studied. The ventricular rate was slowed in all cases. The $R-T$ and $S-T$ segment changes as just described appeared in all 4 cases.

Heart Block. One case with complete $A-V$ dissociation, presumably due to coronary thrombosis, was given urginin. The mechanism changed to a sinus mechanism with a prolonged $P-R$ interval. The change was considered a coincidence.

There were 2 cases of left bundle-branch block in the series. The urginin showed no effect upon the contour of the $Q-R-S$ complexes but the $R-T$ and $S-T$ segments became concave and convex in all leads. In 1 patient with bundle-branch block the mechanism changed to auricular fibrillation, with left axis deviation, and with the T waves in the same direction as the main deflections. The $Q-R-S$ complex originally measuring 0.16 second was changed to measure 0.12 second with disappearance of the notching. Eight days after cessation of the medication the sinus mechanism was resumed with characteristic left bundle-branch block. Repetition of the drug in lesser amounts failed to reproduce this phenomenon.

Auricular Flutter. One case of the series had a chronic auricular flutter. Previous to the study the patient had been treated with quinidin, digitalis and a combination of both without results. During the urginin medication short periods of auricular fibrillation were observed. Paroxysmal periods of sinus mechanism then occurred and the patient eventually resumed a permanent sinus mechanism.

Production of Cardiac Irregularity. In 12 of the 25 cases, extrasystoles were noted. The origin was ventricular in 5 instances, both ventricular and auricular in 4, ventricular and nodal in 2, and nodal alone once. Three of these patients showed extrasystoles both before and during the medication periods. Nausea was observed in only 2 of the 25 cases as an indication of overdosage.

Five cases developed auricular fibrillation during the period of medication. One case (formerly converted from auricular fibrillation to a sinus mechanism with quinidin sulphate) reverted to auricular fibrillation under urginin without quinidin. A second case developed auricular fibrillation on the second day after the onset of bronchopneumonia and the arrhythmia persisted until death on the fourth day. A third case developed auricular fibrillation on the fifth day of medication receiving 3 mg. per day, sinus mechanism was resumed in 48 hours. This patient receiving digitalis (3 grains per day) developed auricular fibrillation at the end of 7 days (total, 21 grains). Cessation of the drug was followed by resumption of a normal sinus mechanism. This phenomenon was repeated on 4 occasions with digitalis. One patient developed

auricular fibrillation on the third day of medication after receiving 9 mg. of urginin (3 mg. per day). The medication was stopped for 3 days and again resumed for a period of 7 days at the same dosage. At the end of another 7 days; sinus mechanism was resumed. The patient was later given 2 mg. per day without change in mechanism. One patient developed auricular fibrillation after 12 days with a dose of 2 mg. per day. This patient had a complicating bronchopneumonia.

Summary. The effects of squill glucosids upon the electrocardiogram appeared to be characteristic and fairly consistent, particularly upon the *R-T* and *S-T* segments. The recorded changes of concavity and convexity produced were similar to those produced by digitalis as reported by Cohn and Pardee. In those patients whom we studied with both urginin and digitalis the changes produced were similar with equivalent amounts of each drug over equal periods of time.

There was a wide variation in the degree of effect produced in different patients, implying a variable amount of absorption of the ingested drug, a difference in the response of the patient, or other unknown factors.

In therapeutic doses, which is a relative term varying with each patient, the effects of urginin, like those of digitalis, appeared to be limited to an effect upon the *R-T* or *S-T* segment, slight prolongation of the *P-R* interval and occasional extrasystoles.

In patients intolerant to the medication, the effects of overdosage appeared to be the production of frequent extrasystoles, marked prolongation of the *P-R* interval and the production of auricular fibrillation.

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THE RÔLE OF THE LABORATORY IN THE DIAGNOSIS OF GALL BLADDER DISEASE.

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IN the diagnosis of gall bladder disease the laboratory has come to be of inestimable help and often takes precedence over the history and physical findings in confirming or denying the opinion. The mimicry of the gall bladder picture by extrabiliary tract conditions has long been recognized. Yet, the very recent statement by Graham and Mackey,¹ that "it is perhaps not sufficiently appreciated that many conditions are often confused with gall bladder disease," reiterates the need for a highly critical attitude on the part of the diagnostician and a thorough investigation of every patient suspected of having gall bladder disease, in order that the operations unwisely performed upon the biliary tract may be avoided.

It was thought that it might be of interest to study a group of patients suspected of having gall bladder disease, in which duodenal drainage was uniformly performed and interpreted, in order to determine to what extent the results of such investigation could be relied upon. To this end, non-surgical biliary drainage was in all cases performed by one of us (H. S.). Microscopic examination of the bile so obtained was made by the same individual and an opinion of the biliary tract findings rendered independently of the historical data and without knowledge of the Roentgen ray report. A single drainage only was done in each patient. Very careful roentgenologic technique and expert roentgenologic opinion were

available for each case, although the Roentgen examination and the interpretation of the films were not done by the same individual. All patients were referred to Surgical Service E, of our University Hospital, so that a uniform surgical opinion would be available. Of further interest is the fact that in 21 of the 30 cases in this series, the gall bladder bile obtained at operation was studied by a group thoroughly familiar with analytical bile chemistry, thus making the data available as a measuring rod for the pre-operative laboratory and the operative findings.

The usual pathologic examination was done on all cases in which the gall bladder was removed, even though the inadequacy of a pathologic examination in showing the degree of disordered function, or even to assure its presence, is well known. Graham and Mackey¹ recently indicated the precise value of this examination in establishing the status of the removed gall bladder. "The surgeon, if he finds little evidence of a pathologic change at the operation, is likely to find solace and justification in the microscopic examination of the organ. Unfortunately, however, this examination is unlikely to be of much help in just those cases in which the help is most needed. It is well known, for example, that there is practically no agreement among pathologists as to what constitutes a normal gall bladder. It is rare, therefore, for a gall bladder to be pronounced normal on the basis of a microscopic examination."

For the diagnosis of inflammatory disease of the gall bladder, gastroenterologist and roentgenologist both rely upon recognizable changes in the same two functions of the organ, its ability to absorb water and its ability to empty its contents. The gastroenterologist's definition of normal gall bladder function depends upon his ability to obtain an adequate gall bladder fraction of bile, of proper concentration, after inducing duodenal relaxation.*

The Roentgen interpretation of normality depends for its success upon concentration of the dye and upon the changes in the size of the shadow as a result of emptying subsequent to the administration of a fat meal. The biliary drainage studies depend in part upon the ability to obtain a gall bladder fraction. When this is obtainable the experienced investigator should be able, as a rule, to indicate derangement of function with as much certitude as can the roentgenologist from a cholecystogram.

In the bile obtained by non-surgical biliary drainage, an alteration of the gall bladder function will be reflected in an inadequate amount of "B" bile, in an imperfectly concentrated "B" fraction, or in a complete absence of a "B" fraction. This last may be indicative not only of abnormal function, but also of cystic duct occlu-

* An adequate "B" fraction (of Lyon) consists of 30 to 50 cc. of dark brown, black brown, or green black bile, showing in the drainage collected a clearly marked difference from the fraction obtained before the so-called "duodenal stimulation" and followed again by a lighter portion.

sion or of a functioning or abnormally functioning gall bladder filled with stones.

In 1923, Hollander⁸ reported cholesterol crystals in gall bladder bile in cholelithiasis. This was confirmed by Mateer and Henderson,⁹ Einhorn¹⁰ and Jones.¹¹ The latter 2 reported cases in which bilirubin calcium pigment, in addition, had been found in the duodenal aspirate. In 1928, Piersol, Bockus and Shay⁷ stressed the significance of these microscopic findings in the bile in gall stone disease. Further experience in a series previously reported,¹² and in this group of patients, has fortified the confidence placed in the finding of cholesterol crystals and characteristic pigment in bile obtained by the Lyon method of non-surgical biliary drainage. Briefly, the presence of both cholesterol crystals and supposed calcium bilirubinate in drainage bile, in our experience, has been invariably associated with the presence of gall stones. The finding of one of these elements alone strongly indicates the presence of stones. When only cholesterol crystals are found, cholesterosis without stones will occasionally be discovered at operation. When the pigment alone is present, the diagnosis of stones must be more cautiously considered, particularly if jaundice is, or recently has been, present. The absence of these elements in the bile when no "B" fraction is obtained, makes it impossible by drainage alone to determine the presence or absence of stones. In such instances stones may be present, but due either to cystic duct occlusion or the failure of the gall bladder to empty, no evidence of their presence may be found in the drainage bile.

Rafsky¹³ recently suggested that the importance of these microscopic findings lies in their quantity. However, we believe that the certain identification of a few cholesterol crystals and minute amount of the characteristic pigment is as significant as the findings of large quantities of each.

This report is based upon the data obtained in patients with gall bladder disease, all of whom came to operation. In Chart I are given the findings as reported from gall bladder drainage and cholecystography.

CHART I.—DIAGNOSIS OF STONES BASED ON THE ROENTGEN AND DRAINAGE FINDINGS:
STONES PRESENT 21, STONES ABSENT 9.
PRE-OPERATIVE DIAGNOSIS.

Roentgen ray.	Bile drainage.	Roentgen ray.	Bile drainage.
10 stones	17	2* stones	1*
2 uncertain	3	7 no stones	8
9 no stones	1		

* A case in which pigment alone was found in the drainage following a severe attack of biliary colic.

The advantage of microscopic study of biliary drainage fluid, over cholecystography in the diagnosis of stones lies in the fact that the experienced microscopist can find definitely formed elements which

even in minute quantities indicate the presence of calculi, while the roentgenologist is dependent upon a contrast in shadows in the gall bladder area. Obviously, the Roentgen criteria are subject to more disturbing variables than the microscopic ones. We do not wish to imply that by non-surgical drainage stones are invariably diagnosed. One case (S. T.) in the series, which did yield a small but definite "B" fraction, failed to show either crystals or pigment in the bile, yet stones were found at operation. Like many other laboratory tests a positive result may be accepted with greater certainty than a negative one. Persistence and care are required even by the very experienced microscopist. Examination of the sediment after centrifugalization should always be made before the specimen is to be considered negative and it is of great importance that the material be examined shortly after it is obtained.

Diagnostic drainage is of value in cases of common duct stone after cholecystectomy. We² have previously recorded such a case and in this series there is another such instance.

Case Abstract. I. C., female, aged 55, had a cholecystectomy in 1927. Six years later she suffered a recurrence of attacks of epigastric pain, nausea and vomiting. There was no jaundice. Cholecystography did not yield any additional information. In the bile obtained by non-surgical drainage numerous clumps of typical pigment were found. In the absence of jaundice, a diagnosis of stone in the duct could be made from this finding in the bile. At operation, a bullet-shaped black stone was found in the common duct measuring about 1 cm. in length and 0.5 cm. in diameter.

Of particular interest in this series has been the availability of the chemical data obtained by the analysis of the bile removed from the gall bladder at operation. As a result of the studies by Ravdin, Johnston, Riegel and Morrison,³⁻⁶ on the fate of the various liver bile constituents in the healthy and diseased gall bladders, criteria are at hand by which the disturbed gall bladder physiology can be measured.

Ravdin¹⁴ and his associates have studied in detail the changes produced in the normal gall bladder in the bile constituents brought to it from the liver and have shown how the various stages of gall bladder disease effect these changes. While significant alterations may be produced in all the bile constituents, it was found that in general the concentration of chlorid and bile salts gives definite indication of the state of gall bladder function.

Compared with the chemical data obtained from an analysis of the gall bladder removed at operation, biliary drainage and cholecystography suffer equally in their attempt to measure gall bladder function. This analysis was made on 21 of the 30 cases in this series (Chart II). With a normally functioning gall bladder, chlorid is rapidly absorbed from the liver bile brought to the gall bladder, the mean concentration being about 10 milli-equivalents per liter. Bile salts, on the other hand, are concentrated, so that

normal gall bladder bile contains approximately 200 milli-equivalents per liter. Damage to the gall bladder may result merely in a retardation of the rates of absorption and concentration, or, in severe damage, in an actual reversal of the normal process so the substances

CHART II.—THE COMPARISON OF CHOLECYSTOGRAPHY, BILE DRAINAGE, AND ANALYSES OF BILE OBTAINED AT OPERATION, WITH OPERATIVE FINDINGS.

Case.	Bile drainage.			Cholecystography.		Bile chemistry.		Operation.
	G. B. function.	Crystals.	Pigment.	G. B. function.	Stones.	M. eq/L Cl.	M. eq/L B. salts.	
F. P.	Cystic duct obs. non-funct.	—	—	Not stated	Pos.	126.8	None	Cyst. duct obs. stones.
B. W.	Normal	Pos.	Pos.	Impaired	?	90.3	22.0	Black bile; stones.
F. G.	Non-function	Pos.	Pos.	Non-function	—	119.8	14.0	Stones.
R. A.	Partial	Pos.	Pos.	Partial	Pos.	No sample	51.0	Stones.
M. L.	Cystic duct obs. non-funct.	—	—	?	—	134.2	Pink	Hydrops; stones.
F. S.	Non-function	—	Pos.	?	—	111.6	Yellow	Colorless B.; stones.
S. T.	Good	—	—	Partial	—	58.7	Faint blue	Black bile stones.
S. F.	Poor	Pos.	Pos.	Poor	Pos.	76.7	33.0	Distend. G. B.; stones.
M. B.	Poor	—	—	Normal	—	54.0	47.0	G. B. thickened.
M. Br.	Non-function	Pos.	Pos.	Partial	Pos.	37.5	27.0	Stones.
E. F.	Partial	Pos.	Pos.	Normal	?	59.8	42.0	Stone.
P. K.	Poor	Pos.	—	Non-function	?	56.6	69.0	Stones.
T. E.	Non-function	Pos.	Pos.	Non-function	Pos.	44.8	23.0	Stones.
M. L.	Normal	Pos.	Pos.	Not stated	Pos.	53.3	2.0	Stones.
E. O.	Normal	Pos.	—	Normal	—	61.5	70.0	Dark bile; stones.
H. H.	Cystic duct obs. non-funct.	—	—	Partial	Pos.	120.0	Faint blue	Hydrops; stone.
M. F.	Normal	—	—	Normal	—	No sample	Red	Dark bile; no stones.
M. S.	Poor	—	—	Poor	—	71.0	71.0	No stones.
L. W.	Non-function	—	Pos.	Non-function	—	No sample	Red	Stones.
M. A.	Normal	—	—	Partial	Pos.	41.0	134.0	No stones.
L. M.	Partial	—	—	Partial	—	115.9	7.0	No stones.

CHART III.—DATA OBTAINED WHERE DRAINAGE OR CHOLECYSTOGRAPHIC STUDIES INDICATED NORMAL FUNCTION.

Case.	Gall bladder function by bile chemistry.				Gall bladder bile at operation.
	Drainage.	Roentgen ray.	Chlorid.*	Bile salts.*	
B. W.	Normal	Impaired	90.3	22.0	Black bile; stones.
M. B.	Poor	Normal	54.0	47.0	G. B. thickened.
E. F.	Impaired	Normal	59.8	42.0	Stone.
M. L.	Normal	Not stated	53.3	2.0	Stones.
E. D.	Normal	Normal	61.5	70.0	Dark bile; stones.
M. F.	Normal	Normal	Red	Dark bile; no stones.
M. A.	Normal	Impaired	41.0	134	No stones.
S. T.	Good	Partial	58.7	Faint blue	Black bile; stones.

* Milli-equivalents per liter.

hitherto absorbed are poured into the bile, while substances that are normally concentrated are absorbed. These changes in the above two constituents result in an increasing concentration of chlorid and in a decreasing concentration of bile salts in progressive gall bladder disease. In all the gall bladder biles studied in this

series, there were definite evidences of gall bladder disease. In 13 of the 21, where the bile was studied by drainage a normal "B" fraction was not obtained and the cholecystographic studies also disclosed evidence of impaired concentration or emptying. But in 8 cases, drainage or cholecystography, or both, indicated a normally functioning gall bladder (Chart III). This is of interest because it shows the weakness of both methods in yielding criteria that definitely establish the normality of gall bladder function. The same criticism applies here as is directed at the attempt to measure liver function by a single functional test. The microscopy of the bile as obtained during drainage, has the advantage over the Roentgen ray, of permitting an examination of the bile crystallography and cellular débris. It would appear from a study of the chemistry of the gall bladder bile, that changes in concentration of the bile constituents may occur while the water-absorbing mechanism is sufficiently retained to produce adequate concentration of the dye in cholecystography, or concentration of the bile pigment to yield a so-called normal "B" fraction by drainage.

From a comparison of the non-surgical biliary drainage of Lyon and cholecystography, it has been our experience that the former is, as a rule, more effective in the diagnosis of gall stones. From the chemical data, it is obvious that a certain diagnosis of a normally functioning gall bladder can be had from neither procedure. One must remember that normal function of a gall bladder as measured by our present laboratory procedures pre-operatively does not preclude the presence of stones. In only 2 instances did both methods indicate a normal gall bladder. Patently, then, from the standpoint of the laboratory, a combined study of the bile, the result of non-surgical drainage and cholecystography, offers the most refined pre-operative diagnosis for gall bladder disease at present. Should it become possible to apply the data obtained from the chemistry of the recovered bile during non-surgical biliary drainage pre-operatively, we should then have the "open Sesame" to the diagnosis and understanding of gall bladder disease.

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THE EFFECT OF ERGOTAMIN TARTRATE ON NON-MIGRAINOUS HEADACHES.*

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EXPERIENCE of the last few years has demonstrated that individual attacks of migraine headache can ordinarily be aborted by the use of ergotamin tartrate.¹ In the experience of two of us, the parenteral administration of the drug has stopped the initial headache treated in 90% of the patients.² In most of these patients headaches were severe and unaffected by the usual sedative drugs. The important question arises whether ergotamin tartrate is of specific value in migraine. If specific, an understanding of its action should shed light on the mechanism producing migraine headaches. If not specific, ergotamin tartrate should prove a headache panacea.

The literature is of little assistance. Trautmann³ states that non-migrainous headaches are not helped by ergotamin but presents no detailed evidence. In this communication we present data which we have collected during the past 2 years.

* This investigation was aided by a grant from the Josiah Macy, Jr., Foundation. The ergotamin tartrate (Gynergen) used was supplied by the Sandoz Company.

Materials and Methods. Our classification of migraine headaches has been a liberal one; recurring headaches with two or more of the satellite symptoms of hemicrania, family history, nausea and vomiting, visual aura, vasomotor symptoms, and failure of relief by ordinary means.

The non-migrainous headaches were those to be encountered on a neurologic service. Patients with psychoneurosis were excluded. Headaches were associated with the following conditions, namely, 8 patients with aseptic meningitis, of whom 7 had had subarachnoid injection of air, and 1 a subarachnoid hemorrhage; 6 patients with increased intracranial pressure, of whom 5 had brain tumor and 1 subdural hematoma; 7 patients with subnormal intracranial pressure following removal of spinal fluid; 8 patients with postconvulsive headache; 1 with sinusitis; 11 in whom the cause of the headache was not ascertained, and 5 in whom the headache was artificially induced by means of histamin phosphate injected intravenously. In the last named group the following procedure was used. Sufficient histamin to produce headache (0.1 to 0.2 cc. of a 1 to 1000 solution) was injected intravenously and the severity and duration (only a minute or two) of the resulting headache noted. After an interval of 20 or more minutes, ergotamin tartrate (0.25 to 0.5 mg.) was injected and 20 to 45 minutes later the previous dose of histamin was repeated.

Ergotamin tartrate was given to these patients in the same manner as to patients with migraine, namely, 0.5 mg. intravenously or subcutaneously. Besides the patient's statement of the effect on the pain, record was kept of the occurrence of nausea and vomiting, and of changes in blood pressure and pulse rate.

Results. The effect on the headache in these 46 patients, and comparison with the effect on the group of 120 migraine patients reported by two of us² was as follows:

	No. of patients.	Percentage with headache.		
		Stopped.	Unchanged.	Worse.
Non-migrainous patients	46	15	63	22
Migraine patients	120	89	8	3

There is thus a sharp contrast in the therapeutic effect in the two groups of patients. Ergotamin caused complete relief of headache in 89% of migraine patients and in only 15% of the other group; it made the existing headache worse in 3% of the migrainous and in 22% of the non-migrainous group. This difference in degree would seem to constitute a difference in kind. By and large, ergotamin helps only patients with migraine.

Study of the results in the various conditions represented in the non-migrainous group shows that, of the 7 patients relieved, 3 were in the group of 11 headaches of unknown cause (27% relief) and 3 were in the group of 8 postconvulsive headaches (37% relief). The large proportion of epileptic patients who were relieved brings

to mind the supposed underlying relationship of epilepsy and migraine, though more important may be the fact that postconvulsive headaches are naturally short lived. If our investigation had been carried on in a medical ward with "ordinary" spontaneous headaches, probably the percentage of cases relieved would have been higher than the observed 15% (though of the 10 subjects made worse by the injection, 5 belonged to this same unknown group, and 2 to the postseizure group). In none of the 5 cases given histamin did ergotamin lessen the severity or duration of the resulting headache.

Not only is ergotamin of little account in stopping non-migraine headaches, it may, according to Barger,⁴ initiate a headache. To test this point we administered the drug to 38 subjects who were at the time free of pain in the head. Six (16%) of the subjects complained of resulting mild headache.

Aside from its effect on headache, the most prominent sequelæ of ergotamin administration are nausea and vomiting. The comparative incidence of gastric symptoms in the three groups of subjects was as follows:

	Number.	Percentage having	
		Nausea.	Vomiting.
Without headache	38	47	18
Non-migrainous headache	46	56	37
Migraine	89	77	60

The epigastric discomfort of some of the subjects was too indefinite to be called nausea. Vomiting, when it occurred, was an objective symptom and in the headache groups bore some direct relationship to the proportion experiencing relief. However, in individual cases, there was no constant relationship between relief of headache and the presence of gastric symptoms.

Blood pressure and pulse rates were not recorded in all cases. As in migraine patients, the majority of patients with other types of headache or with none, had an increase in systolic blood pressure and a decrease in pulse rate, but changes in pressure and in pulse rate did not seem to be related to the therapeutic effect of the drug.

Comment. Quinin is called a specific against malaria, though it does not invariably stop malarial paroxysms and though it may favorably affect non-malarial fever. In the same sense, ergotamin tartrate may be spoken of as a specific for the relief of migraine headache. It evidently interrupts the morbid process which results in pain in the head, chilliness and malaise.

What is this morbid process? Beginning with Trautmann,³ various authors have spoken rather glibly of an antagonistic effect of ergotamin on overactivity of the sympathetic nervous system. This might be conceived of as a release of spasm of cerebral vessels or as a direct action on sensory nerve endings. It is true that injection of ergotamin tartrate is followed by an increase in cerebro-

spinal fluid,⁵ in systemic blood pressure and in cerebral blood flow,⁶ but none of these changes seems sufficient in itself to explain the relief afforded.

It is possible that there is abnormal behavior of bloodvessels of the dura mater which does not show in records of total cerebral blood flow or of intracranial pressure, and that ergotamin might influence the dural vessels or the nerves which carry impulses from them. Evidence in favor of this view is the observation of Pool and Nason⁷ that ergotamin in cats caused constriction of arterioles of the skin and dura, but not those of the pia. Pickering⁸ believes that the severe throbbing headache which follows histamin injection arises in the bloodvessels in the dura, for removal of the Gasserian ganglion on one side anesthetizes the dura and prevents the appearance of histamin headache on that side. Less convincing is the clinical evidence of Dickerson,⁹ who "cured" hemicrania by ligation of the middle meningeal artery on the side affected, and of Penfield,¹⁰ who secured relief for 2 migraine patients by section of the ophthalmic fibers of the Gasserian root, the chief nerve supply to the dura (after superior sympathectomy had failed).

The evidence gained from our own experience has not supported the hypothesis of ergotamin as a paralyzer of the sympathetic nervous system. One patient had had interruption of accessible sympathetic pathways without relief of pain; yet ergotamin stopped her individual attacks. One of us¹¹ has observed that relief of migraine headache by ergotamin is not attended by alteration of sympathetic activity as judged by measurements of the electrical resistance of the skin.

If Pickering is correct in his belief that histamin headache arises in the vessels of the dura and if this is the point of origin of migraine headache, ergotamin tartrate should be effective in preventing or modifying histamin headache. It failed to do this in the cases tested by us, and by Pickering (personal communication). As a further test we injected histamin into 4 migraine patients whose attack had just been aborted by ergotamin. In every case a characteristic throbbing, short-lived histamin headache occurred.

Summary. Ergotamin tartrate is about 90% effective in aborting individual migraine headaches. The drug was injected into 46 patients having a non-migrainous headache; 15% were relieved; 63% were unrelieved, and 22% were made worse. Of 38 persons without headache who were given the drug, 16% developed a headache.

Nausea and vomiting occurred less frequently in persons having a non-migrainous headache or none, but in individual cases the effect of ergotamin on headache could not be related directly to the presence of gastric symptoms.

In 4 migraine patients relieved of headache by ergotamin, injection of histamin produced the usual histamin headache.

Ergotamin tartrate has a specific action in headaches of the migraine type. The evidence at hand indicates that the action is not directly on sensory nerve endings in the dura or skull, but that there is an intermediate systemic action.

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COMPARISON OF PROLAN BIOASSAYS IN TERATOMA AND OTHER CONDITIONS.*

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THE purpose of this report is to present an analytical study of the conditions associated with an increased urinary output of the sex hormones (prolan A and prolan B), with special reference to teratoma testis. Emphasis is placed on the clinical value of these biologic hormone assays.

The results presented in this study are based upon over 500 completed tests necessitating about 15,000 accurately spaced and measured intraperitoneal injections into approximately 3000 mice.

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The Aschheim-Zondek reaction is now widely used in the diagnosis of pregnancy. Recently, however, the principles of this assay have been applied as a diagnostic aid in teratoma testis. Single case reports showing excessive urinary prolactin output associated with teratoma testis exist in the literature: Heidrich and Fels,¹ Kantrowitz,² Lilienthal,³ Pachkis,⁴ Hady,⁵ Bollag,⁶ Weinstein and Schofield,⁷ and Johnson and Hall.⁸ Reports of series of cases have been presented by Zondek,⁹ Ferguson,¹⁰ Stelle,¹¹ Owen,¹² Herger and Thibaudeau,¹³ and by Cutler and Owen.¹⁴

Technical Consideration. Qualitative determination of the sex hormones in the urine, other body fluids, or extracts as applied in the diagnosis of pregnancy consist of injecting such fluids into suitable test animals and at a later date examining the sex organs for changes. Aschheim¹⁵ employed immature female mice, Friedman¹⁶ used non-pregnant rabbits, Brouha *et al.*¹⁷ suggested male mice, while Curtis and Doisy¹⁹ use adult oophorectomized or immature female rats. Recently Kanter *et al.*¹⁸ reported a small fish, the bitterling (*Rhodeus amarus*) as a suitable test object.

TABLE 1.—THE RABBIT-MOUSE CORRELATION VALUES INDICATING THE LIMITATIONS OF THE RABBIT TEST FOR TERATOMA TESTIS.

Case.	Rabbit test.	Mouse test.
A	Negative	500
B	Negative	200
C	Questionable	2,000
D	Negative	2,000
E	Negative	1,000
F	Negative	500
G	Positive	2,500
H	Positive	16,000

Rabbit tests in this series all by single intravenous injections of 10 cc. of fresh urine. The mouse test results are stated in mouse units per liter of urine; 200 or above mouse units constitute a positive indication of teratoma testis.

To provide comparative results it is essential to have an assay capable of giving quantitative findings. The single rabbit test is but a qualitative assay. Since the majority of urines from patients with teratoma assay less than 2000 mouse units per liter, the usual rabbit test employing a single injection of 10 cc. or less of urine would be negative, as has been shown in this laboratory (Owen and Cutler²⁰). Results obtained in this laboratory show the fish test to be inaccurate and similar findings are reported by Kleiner *et al.*²¹ and by Szusz.²² The immature female mouse is a serviceable test animal, as has been shown by Ferguson,¹⁰ Owen,¹² and others. Approximate comparison dosage ratios for the various test animals have been determined. For the prolans and other water-soluble endocrins of like nature the dosages vary in proportion to the animal weight with the exception of fish.

A complete description of the assay procedure used in this study is given by Cutler and Owen.¹⁴ Essentially such assay employs

6 immature female mice. By means of appropriate extracts a dosage range of 0.5 to 10 cc. of urine is obtained. Due to the double effect of follicle stimulation and luetinization, the readings of the test give the following quantitative determinations of the prolans in mouse units per liter of urine: 100, 200, 400, 500, 1000, 2000, 2500, 5000 and 10,000.

We have found that morning urines from teratoma patients are apt to contain more hormone per liter than do samples from the 24-hour outputs. Davy and Nason²³ have noted similar findings for the urine from pregnant women. Since the total amount of hormone actually excreted varies but slowly, it is necessary to obtain the volume of the 24-hour-output and to use a fractional part of this for assay purposes whenever possible. With this information calculation of the total daily output of hormone is facilitated and errors in the amount of hormone per liter of urine are avoided.

TABLE 2.—SHOWING THE DOSAGE RATIO IN MOUSE UNITS FOR THE VARIOUS LABORATORY TEST ANIMALS COMMONLY USED.

Subject employed.	Mouse units for positive.	Reference source.
Mouse	1	
Rat	10	Lewis and Geschikter.
Rat	3	Gardner <i>et al.</i>
Rabbit	22	Owen.
Fish, male	4 to 10	Calculated from Kanter <i>et al.</i>
Fish, female	8 to 16	Calculated from Kanter <i>et al.</i>

Spoilage or decomposition of the urine does not seem to affect the hormone materially, but such urines are apt to be toxic to the laboratory animals. A suitable preservative should be employed. The specimens mailed to the laboratory contain 1 drop of tricresol in 2 ounces of urine.

Conditions Associated With Increased Urinary Prolan Output. Conditions other than pregnancy and teratoma have been associated with an increased urinary prolans output. Chorionepithelioma in the female as well as in the male is usually accompanied by excessive amounts of urinary prolans (Fortner and Owen²⁴). Hirsch-Hoffman²⁵ reported 3 cases of cerebral tumors and a case of acromegaly in females showing positive prolans findings. Kraus²⁶ cites Biedl and Morgetay-Becht as finding positive prolans assays in two-thirds of the acromegaly cases studied. He also reported 19 of 29 cases of elevated intracranial pressure as showing a positive urinary prolans test. Ziserman²⁷ lists hyperthyroidism and other conditions in the female as liable to give false positive pregnancy tests. Zondek²⁸ cites castration as showing occasional false positives. Castration either by surgery or by Roentgen rays may cause false positive reactions and, although prolans A (follicle stimulating hormone) may be present, the urines of castrates are said not to contain

prolan B (the luteinizing factor). Dodds²⁹ states that castration results in an increase in the amount of anterior pituitary hormone in the patient's blood. He also cites 4 instances of pituitary gland tumors as giving negative assay findings. Ehrhardt³⁰ lists rapidly proliferating tumors as myoma, carcinoma and genital hypoplasia as giving false positive pregnancy test. Maser and Hoffman³¹ state that compensatory pituitary hyperfunction accompanying sexual deficiencies may give rise to false positive pregnancy tests.

In spite of so many possible interfering conditions, it is generally accepted that the usual Aschheim-Zondek reaction gives above 90% correct findings in the diagnosis of pregnancy (Aschheim,¹⁵ Dodds,²⁹ Weisner³² and others).

TABLE 3.—DISPLAYING THE PROLAN A FINDINGS IN NON-TERATOMATOUS PATIENTS. THE ASSAYS ARE GIVEN IN MOUSE UNITS PER LITER OF URINE.

Cases.	Diagnosis.	Quantitative assays.				
		Negative.	100.	200.	400.	500.
6 . . .	Cyst, testis	11	1	2	1	
2 . . .	Luetic	4				
1 . . .	Myxosarcoma	2				
1 . . .	Granuloma	2	2	1
1 . . .	Lymphosarcoma	1				
1 . . .	Ca. prostate	1				
1 . . .	Pseudomyxoma	5	..	1		
2 . . .	Pituitary dysfunction	2				
1 . . .	Gynecomastia	2				
5 . . .	Epididymitis	7	1	3		
1 . . .	Lymphoma	1				
4 . . .	Mixed tumor, parotid gland	8				
1 . . .	Squamous cell, keratinizing	2				
1 . . .	Paraffinoma	2				
1 . . .	Sacrocoecygeal teratoma	3				
29		53	4	6	1	1

All positive tests were obtained on 4 cases: 1 cyst, 1 granuloma, 1 pseudomyxoma, 1 epididymitis. Serial checks on 3 of these cases gave consistent positive assays.

Many of the conditions which may interfere with the interpretation of the reaction occur in females; consequently, the possibility of false positive is minimized in males. The control series at this laboratory and others include over 500 negative assays on urines from normal males and from patients suffering with benign lesions of the testis (Cutler and Owen¹⁴).

The assay as planned approaches closely the findings associated with normal urines and it may be expected that incorrect positives will only be avoided by conservatism in interpretation of the results. Occasional false positives in the higher range mouse dosages were expected. It became necessary to qualify the interpretation, *viz.*, unless the 2 mice receiving the highest dosages are positive the test is questioned and repeated at a later date. One quantitatively low positive assay of itself is not wholly indicative of teratoma, but if a series of tests are positive and the quantitative results show

an increase in hormone, then the diagnostic value of the test is rarely to be questioned.

Results. In 71 cases later proven histologically to be teratoma, the findings in 340 tests ranged from negative (less than 100 mouse units per liter of urine) to 125,000 mouse units per liter of urine in a case of chorionepithelioma testis. Omitting 2 cases of chorionepithelioma testis the average finding was approximately 950 mouse units per liter of urine. Of the 71 cases of known teratoma, 69 showed one or more of the following conditions: a drop in the urinary prolan excretion following irradiation or surgery, an increased output on series tests, or tests consistently above 200 mouse units per liter of urine. Two patients with no pre-operative prolan test showed a negative postoperative prolan assay. Of the 69 cases, 37 showed an increased prolan finding on series tests, 51 displayed a drop in urinary prolan following irradiation or surgery; 26 showed tests consistently above 200 mouse units per liter of urine. In 17 instances following irradiation and/or surgery the test dropped to negative, while in 39 cases the post-treatment prolan dropped to 200 or less mouse units of prolan per liter of urine. In 7 instances irradiation therapy failed to cause a drop in prolan excretion. In 6 cases coming to autopsy the findings have verified the prediction of widespread metastases as indicated by the excessive prolan output, previous to death.

On 29 patients with pathologic conditions other than teratoma located in the testes 64 tests revealed 3 instances of false positives. These false positives occurred in 1 instance each of cyst, epididymitis and granuloma. All 3 cases had previous orchidectomies, thus the findings may be due to the partial castration. The percentage of false positives is less than 10.

Of 25 other cases now in process of diagnosis, clarification reveals 16 are definitely negative and 9 have positive assays ranging from 200 to 50,000 mouse units of prolan per liter of urine.

A majority of our cases have had orchidectomies at other hospitals previous to their admission here for treatment; yet the prolan assay usually decreases following the irradiation therapy, demonstrating that the test might be used as a means of detecting metastases as well as the original teratomas.

Comment. The assay of urinary prolans in cases of teratoma testis adds a practical diagnostic aid to the armamentarium of the laboratory. Since irradiation of such tumors is followed by a decrease in the urinary prolans in the majority of cases, the effectiveness of treatment may also be judged. The test thus serves as a guide in the diagnosis, prognosis and treatment of teratoma testis.

False negatives or false positives have occurred in less than 10% of the assays in this series, indicating that the assay as planned and conducted is as suitable a diagnostic aid for teratoma as the original less quantitative Aschheim-Zondek reaction is for the diag-

nosis of pregnancy. By careful interpretation and serial tests it is possible to increase the accuracy of the assay as a diagnostic aid.

The routine use of the bioassay at this hospital has demonstrated its practical value. Over 125 suspected teratoma testis cases have benefited by the findings of the test. The laboratory now serves as a testing center for the various Veterans' Administration Facilities as well as for the patients hospitalized here. A mailing service for specimens has been instituted to aid in the follow-up of discharged patients.

Summary. 1. Quantitative determinations of the urinary prolans in 125 cases of suspected teratoma testis have been made.

2. In general, patients suffering with teratoma testis excrete more than 100 mouse units of the prolans per liter of urine.

3. False negatives or false positives occur in less than 10% of the cases; thus the test is as accurate as the usual laboratory test.

4. A review of other conditions reported to be associated with excessive urinary prolan output is presented.

5. Original teratomas, local recurrence or metastases are associated with increasing prolan findings as displayed by serial assays.

6. A marked diminution in the prolan output usually follows irradiation or surgery.

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SPONTANEOUS PNEUMOTHORAX SIMULATING ACUTE ABDOMINAL AFFECTIONS.

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SIMULATION of acute abdominal disease of a surgical nature by thoracic affections with referred pain is a matter of more or less common knowledge. The close resemblance at times between lobar pneumonia, acute fibrinous pleuritis, coronary thrombosis, acute fibrinous pericarditis and the "acute surgical abdomen" is emphasized in practically every text. The same can be said regarding lesions of the spine and spinal nerves as osteomyelitis of the thoracic vertebrae, intercostal neuralgia, etc. Other affections of the chest, such as acute cardiac decompensation (producing presumably sudden hepatic engorgement), ruptured or dissecting thoracic aneurysm, pulmonary infarct, acute mediastinitis and spontaneous rupture of the esophagus although infrequently mentioned are also almost universally recognized as mimics of primary abdominal disease.

Spontaneous pneumothorax masquerading as an abdominal affection is apparently regarded as extremely rare by or is not known to most writers, since it is generally omitted in treatises dealing with abdominal and thoracic diagnosis. No reference to pneumothorax simulating the "acute abdomen" can be found in any of the many excellent American texts or systems of surgery. The same is true of continental handbooks. In only one English publication, by Adams,¹ is pneumothorax mentioned among the intrathoracic affections which are capable of producing the picture of an acute abdominal illness. Adams does not, however, cite any specific example. A careful survey of the medical periodical literature leads to the disclosure of only 4 reports, each of which contains the description of one instance of spontaneous pneumothorax where the erroneous diagnosis of primary abdominal disease was made.

There is reason to believe that the incidence of pneumothorax simulating the "acute surgical abdomen" is not as low as the literature seems to indicate. The writers have personally observed in a relatively short period of time, 3 characteristic examples (2 in a large, general hospital and a third in private practice)—the explanation for this rather unique experience lying probably in the frequency with which they resort to the Roentgen ray. In all questionable or atypical abdominal cases, the fluoroscope supplemented at times by plates is employed as part of the routine examination. It is not unlikely that without the aid of the Roentgen-ray the correct diagnosis of pneumothorax might not have been established in some of our cases and the presence of non-existent abdominal disease assumed. Since so few actual instances of pneumothorax simulating acute abdominal affections are recorded, it is deemed advisable to summarize those published by others and to describe briefly the ones observed by ourselves.

Summary of Cases Reported by Others. 1. *Siebner's*² Case. A man, aged 32, experienced extremely severe sudden epigastric pain, occurring while riding to work. The pain which radiated to the left shoulder was associated with nausea. Upon admission the patient appeared to be in "shock." The temperature was 99.5° F. and the pulse 100 per minute. Respirations were shallow and only slightly accelerated. The heart and lungs were normal except for slight decrease of the breath sounds at the left base. The abdomen was boardlike, retracted and very tender. The liver dullness was not obtained with certainty. The diagnosis of perforated peptic ulcer was made and an immediate operation performed. No lesion of the stomach or other abdominal structure was discerned. The following day, the first signs of a left pneumothorax were elicited. Eight days later a Roentgen ray revealed a complete left pneumothorax. The patient passed through an uneventful convalescence, and at the end of the third week, only a small amount of air and fluid remained in the left pleural cavity. The sputum was persistently negative for tubercle bacilli. The patient has been well since.

2. *Beardsley's*³ Case. A young man of 26, while in a tuberculosis ward, was suddenly seized by severe, knifelike abdominal pain. Two hours after the onset the author found the patient sitting in bed with his head bent forward between his knees, groaning with pain and covered with cold perspiration. At first the pain was localized and was situated to the left of the umbilicus but later spread to involve the entire left abdomen. The temperature was subnormal, the pulse 140 per minute, and the respirations only slightly accelerated. One hour after administration of $\frac{1}{2}$ grain of morphin, the patient was comparatively free from pain unless movement occurred. The abdomen was distended, rigid and tender. A diagnosis of perforated tuberculous ulcer was made but the patient's condition did not permit surgical intervention. Except for an increase of the abdominal distention, the patient continued with the same symptoms and signs for 2 days following which he died. At no time was dyspnea present. At autopsy, although there were many tuberculous ulcers present in the intestine, none had perforated and no peritonitis was found. There was, however, a left sided pneumothorax which was the only lesion to account for the abdominal symptoms.

3. *Oechsli and Skillen's*⁴ Case. A woman aged 25, developed during the fourth month of her stay in a tuberculosis hospital, intense epigastric pain,

a severe chill, fever of 103° F., a pulse rate of 125 and a respiratory rate of 28 per minute. The pain was so violent that even morphin gave but little relief, and at onset was associated with nausea and vomiting. The following day the emesis recurred and the pain persisted. No noticeable dyspnea or cough was present. For the next 5 days there was only a slight change in the patient's condition. The pain in the epigastrium continued and was accompanied by occasional slight pains in the left chest. Two days later, extreme hyperresonance was found over the lower left chest and a Roentgen ray showed a collapsed left lung. The patient recovered from the pneumothorax.

4. *Hurxthal's*⁵ Case. A man of 29 had suffered for 2 to 3 years from epigastric discomfort occurring 2 hours or so after meals. The pain was relieved by the ingestion of food and also soda. On June 30, 1928, while attempting to unloosen a seat of his automobile, he experienced a sharp pain in his right shoulder. He took to bed and obtained some relief. After a few hours of bed-rest the patient attempted to drive his car, whereupon an increase of the shoulder pain occurred and dyspnea and abdominal pain appeared. Upon entrance to the hospital, the patient appeared quite ill. The breathing, however, was not labored but there was appreciable cyanosis. The pulse was thready, the rate 120 per minute and the blood pressure was 80 systolic and 70 diastolic. The abdomen was rigid and painful to pressure, especially in the epigastrium and in the right upper quadrant. These observations together with the presence of abdominal pain and a typical chronic ulcer history suggested the diagnosis of perforated peptic ulcer. However, when the chest was carefully examined it was found that the right side was larger and exhibited less respiratory mobility than the left and that over the right chest there was hyperresonance except at the base posteriorly where there was shifting flatness with absence of fremitus and breath sounds. The acute illness was then attributed to a right pneumothorax, the chronic ulcer syndrome apparently being unrelated.

Authors' Case Reports. CASE 1. M. S., a white male of 50, while about to drive a golf ball on June 9, 1929, was suddenly seized with right upper abdominal pain which lasted a few minutes and then ceased spontaneously. He then walked about 200 yards when he experienced a recurrence of the abdominal pain which persisted and became associated with distressful and labored respirations. After a brief period, he was able with assistance to walk back to the club-house and there while dressing he became dizzy and vomited a huge quantity of gastric contents. Following morphin, the patient was transported home. The abdominal pain and dyspnea continued and in addition he vomited 3 times. A physician who saw the patient at his house diagnosed a perforated ulcer. When seen by one of us (H. A. S.) a few hours after onset of his illness, the patient was suffering from severe upper abdominal pain and respiratory embarrassment. The abdomen was slightly distended and moderately rigid and tender especially over the right upper quadrant. The pulse and respirations were accelerated but the temperature was normal. A perforated ulcer seemed plausible.

Close observation of the markedly emphysematous chest elicited that on the right side the respiratory excursion was somewhat limited and that the breath sounds were diminished as compared to the left. There were a few moist and many dry râles throughout both lung fields. A history of a long-standing bronchitis and bronchiectasis was obtained. There had been no previous digestive complaints to suggest ulcer. A diagnosis of right pneumothorax due to a ruptured emphysematous bleb was made and conservative treatment advised. The marked tenderness over the right upper quadrant was ascribed to engorgement of the liver which organ was indistinctly felt below the costal border. The following day the patient's temperature

rose to 102° F. and the physical evidences of a pneumothorax became manifest. A Roentgen ray showed abnormal clarity of the affected side and retraction of the lung characteristic of pneumothorax. No fluid was present in the chest cavity. After 12 days the patient recovered from the pneumothorax.

CASE 2. C. Z.; a man of 37 entered the Cook County Hospital on December 17, 1932 with the following history. On December 11, he contracted a "chest cold," manifested by thoracic pain, cough and expectoration, on which account he remained in bed. During the early morning hours of December 16, the patient was suddenly seized with a very severe, sharp pain in the upper abdomen which caused him to roll about, cry out and moan. The pain seemed to compress his abdominal contents and to shut off his breath. After several minutes, the pain ceased spontaneously but returned in about 20 minutes. Vomiting occurred once at the onset. The abdominal pain recurred at intervals throughout the night. The patient stated that he felt the least pain while he sat upright with his thighs flexed on the abdomen. During the day of December 16, there were persistent soreness in the upper abdomen and vomiting. There was nothing in the past history prior to the onset of the "chest cold" to suggest tuberculosis.

At the time of admission he appeared acutely ill and coughed frequently. The pulse rate was 82, the temperature 98° F. and the respirations 24 per minute. The two sides of the chest moved equally on deep breathing. Over the inferior portion of the right chest the resonance was impaired and the breath and voice sounds greatly diminished. The heart was essentially normal. The abdomen was full in the upper half where both rigidity and tenderness were present. Peristaltic sounds were diminished. The liver edge was felt two fingers below the costal margin. The blood picture was normal except for indications of a secondary anemia. The two physicians who examined the patient shortly after admission were unable to decide whether the abdominal pain was due to a perforated peptic ulcer or to a basal pleuritis. When called upon to attempt the differentiation, the authors fluoroscoped the patient and observed a partial pneumothorax on the right side. A roentgenogram taken the following day (Fig. 1) revealed a greater accumulation of air on the right side and evidence of an old fibro-calcareous tuberculosis on the left. The patient recovered slowly from the acute episode.

CASE 3. D. W., a man of 37, entered the Cook County Hospital on June 28, 1930, with the history that 6 hours previously he was awakened by nausea followed by vomiting. Immediately after the emesis he felt a severe, lancinating pain in the epigastrium which radiated around and upward to the interscapular region of the back. The pain continued severe and even two hypodermic injections of morphin failed to afford relief. The patient preferred the sitting to the recumbent position. Vomiting recurred 3 times. Inquiry into the past history elicited the information that the patient had experienced occasional post-prandial epigastric burning relieved by food and soda. No information was obtained which was suggestive of past or present tuberculosis.

The physical examination disclosed an acutely ill white male with a temperature of 99° F., a blood pressure of 170 systolic and 120 diastolic, and pulse and respiratory rates of 120 and 48 respectively. The tactile fremitus, breath sounds and resonance were found diminished on the left side from the angle of the scapula downward. The abdomen was flat, markedly tender and rigid in the upper quadrants. The liver dullness was apparently unchanged. Peristaltic sounds were greatly diminished. The white cell count was 18,000.

Opinions as to the diagnosis varied. While the advisability of laparotomy

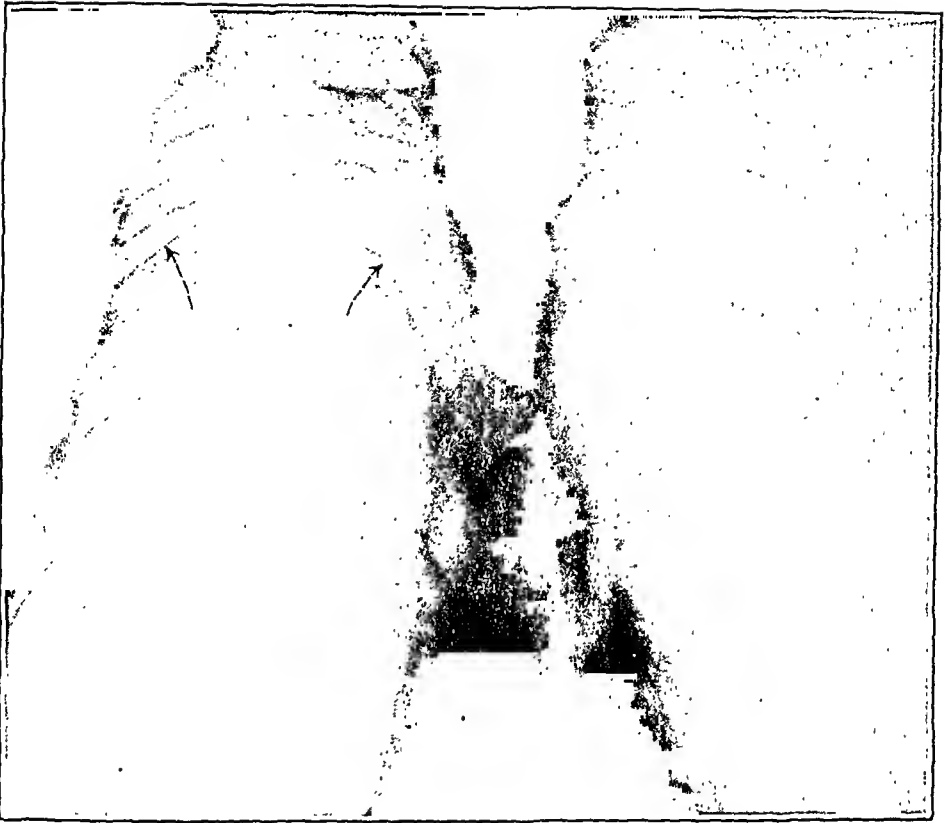


FIG. 1.—Valvular pneumothorax which clinically simulated an acute abdominal affection (authors' case reports, No. 2). The depression of the diaphragm by displacing the liver downward resulted in the presence of tenderness and resistance in the right hypochondrium. Adhesions prevent complete collapse of the right lung and displacement of the mediastinum to the left. The lower border of the right lung is indicated by arrows. Fibro-calcareous, tuberculous markings are observed in the left lung field.

was being discussed, the patient was fluoroscoped and a rather well developed left hydropneumothorax demonstrated. Nothing further could be determined since the patient died 4 hours after entrance and permission for necropsy was refused.

Comment. A study of the foregoing case histories leads to the realization of the difficulty one may encounter in distinguishing a sudden pneumothorax from an acute surgical abdomen. In the first place the clinical picture of rupture of the lung may be chiefly an abdominal one. Intense abdominal pain, nausea and vomiting, associated with tenderness and rigidity which were present in the cases recorded, constitute a syndrome which generally demands immediate laparotomy. Particularly is attention likely to be focussed on the abdomen when a history of previous gastro-intestinal disturbance is obtained, as in 4 of the 8 cases reviewed. In the second place, thoracic symptoms such as occur characteristically in pneumothorax are frequently observed in acute surgical affections of the abdomen. For instance, the occurrence of sudden pain following violent exertion, the reference or radiation of pain to the shoulder region, dyspnea, collapse, and the assumption of the sitting position with the legs drawn upward all are commonly met with in perforated peptic ulcer.

The error of regarding a sudden pneumothorax as an abdominal lesion can almost invariably be avoided. A careful chest examination of each patient with an atypical picture of abdominal disease will eliminate a large percentage of mistaken diagnoses. Unfortunately, only too frequently when the symptoms point to an affection within the abdomen the chest is examined in a perfunctory manner or even neglected altogether. A certain amount of skill in physical diagnosis is often a prerequisite for the correct interpretation of the underlying disease. It is true that an advanced pneumothorax with almost complete collapse of the lung does not require a virtuoso but when the pneumothorax is partial it may elude the most expert. Close attention to the abdominal signs may reveal the tenderness to be merely hyperesthesia and the muscular rigidity to be only apparent and not continuous. However, here again some experience and skill on the part of examiner is indispensable. Of particular value in directing the attention of the physician to the possibility of a pneumothorax is the history of previous pulmonary disease especially tuberculosis.

For the detection of an unrecognized pneumothorax, the Roentgen ray is of extreme importance. When the symptomatology is atypical and the physical signs are difficult to elicit, it is likely that only a small percentage of the instances of pneumothorax are discovered by clinical means. The use of the fluoroscope may suffice to demonstrate the pulmonary collapse but not infrequently proves inadequate. A limited collection of free air may be difficult to identify unless fluid is simultaneously present in the chest cavity.

The resulting fluid level is then readily observed in the fluoroscope and can be made to shift with change in position of the patient. However, the escape of fluid may not occur until late in the course of illness or not at all. It is therefore, necessary in questionable cases to take plates. The exposure is best made at the height of forced expiration in which state the pneumothorax is rendered most apparent. Since sudden pneumothorax tends to simulate most closely ruptured peptic ulcer, the Roentgen ray examination serves a double purpose. The Roentgen ray is capable of demonstrating the presence or absence not only of a pneumothorax but also that of a pneumoperitoneum. Fluoroscopic examination is quite sufficient to detect free intraperitoneal air and requires only a few moments. The value of the Roentgen ray in the diagnosis of perforated peptic ulcer, including details of the technique, interpretation, etc., has been discussed elsewhere (Vaughan and Singer⁷).

Summary. Sudden pneumothorax simulating an acute surgical affection of the abdomen is not a particularly rare occurrence. Three instances have been encountered by the authors. The danger of mistaking spontaneous pneumothorax for a surgical emergency can usually be avoided if the possibility of sudden rupture of the lung is included in the diagnostic considerations. The mere thought of pneumothorax will not always suffice as slight or partial pneumothorax is likely to elude the average examiner. The most effective means of avoiding error is by resort to the Roentgen ray. Fluoroscopy alone may be adequate, especially if a hydropneumothorax is present when a shifting fluid level may be visualized. In many instances however, plates are indispensable for demonstration of the escaped air. The pneumothorax is rendered most apparent when the exposure of the film is made at the height of expiration.

* Since the time this article was submitted for publication, the following report has appeared in print: Joress, M. H.: Spontaneous Pneumothorax (Rupture of the Lung) with Abdominal Symptoms in the Course of Artificial Pneumothorax—A Report of Two Cases, *Am. Rev. Tuberc.*, **33**, 98, 1936. The diagnosis in both instances was rendered less difficult than usual due to the knowledge of a preëxistent pulmonary tuberculosis.

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A METHOD FOR DETERMINING THE SEDIMENTATION RATE AND RED CELL VOLUME IN INFANTS AND CHILDREN WITH THE USE OF CAPILLARY BLOOD.

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THE majority of methods designed for the determination of the sedimentation rate of the red blood cells depends upon the use of venous blood. While the large quantities of blood obtained in this way simplify the manipulation of the test, practical difficulties are encountered when venipuncture is attempted in infants and young children. This is particularly evident when repetition of the test at short intervals is required. In rheumatic disease, for example, in which the determination of the sedimentation rate is utilized as a guide to the progress of the condition, the distress of the young patient which accompanies venipuncture often restricts the number of tests that should be carried out for comparative purposes.

A large number of micromethods, in which capillary blood is employed, has, therefore, been devised in order to overcome these obvious disadvantages, with results approximating those of macromethods. There are several considerations, however, which have interfered with their more widespread use. The employment of minute quantities of blood often requires considerable dexterity and practice. The tendency to clot formation, due to delayed or insufficient admixture with the anticoagulant, results in irregularity of the sedimenting column. An additional factor responsible for discrepancy in results with the two types of tests is the influence of capillarity exerted within the lumen of the narrow tube or pipette, in which the rate of sedimentation is measured, which constitutes an integral part of a micromethod. Another inadequacy is that there is usually no provision for estimating the corpuscular volume percentage, an important factor with rapid rates of sedimentation.

The introduction of another sedimentation tube, in spite of the multiplicity of methods that already exists, therefore seems justified. The purpose of this paper is to present a practical, simplified and reasonably accurate method for estimating the sedimentation rate with the use of capillary blood, which, however, embodies the basic specifications and features of a standard venipuncture method. In a series of observations with the blood of infants and children, the test with few exceptions has proven of definite value as an additional guide in supervising the illness and convalescence of the sick

child. Unexplained results have at times been obtained, but the same situation occurs with any laboratory procedure.

No attempt will be made to review in detail the vast literature concerning the theoretic basis for changes in the suspension stability of blood. It is generally agreed that a rapid rate of sedimentation during the course of infection depends upon an increase of the plasma fibrinogen and globulin with which disease processes are associated. The effect of variations in electric charges on agglutination of erythrocytes is doubtless a fundamental contributing factor.¹ But of more practical importance is the provision that the size and number of the red cells fall within certain limits, since a rapid sedimentation rate occurs in anemic states independent of infection.

Technique. The tube that has been specially designed represents a modification of the features of the Cutler micro-² and macromethods³ and of the Wintrobe tube⁴ used with small quantities of blood. It constitutes in effect a macrosedimentation tube of reduced dimensions rather than a microsedimentation tube of the type in current use since the latter implies apparatus possessing a capillary bore and requiring a single drop of blood. The tube described in this paper (Fig. 1c)* will, however, be referred to as one for microsedimentation since it utilizes capillary blood as contrasted with macrotubes in which venous blood is examined. Its diameter is approximately 2.5 mm., which corresponds to the minimum requirement for the micromethod.^{5,6} It is graduated like the Cutler tube into 50-mm. divisions with a capacity within the measured area of less than 0.25 cc. of blood. Above this zone, the tube is widened into a small cup, the rim of which serves to guide the stem of the pipette with which the blood is transferred from the collecting tube. This feature also facilitates cleansing.

A variety of anticoagulants have been used in sedimentation tests. Although heparin, which is regarded as the ideal substance,⁷ was utilized for comparative tests in this study, a solution of 5% sodium citrate was ultimately adopted because of its availability and its nominal cost. Other concentrations of sodium citrate, as well as mixtures of oxalates, have been suggested by various writers. It was observed, however, that the results with the use of a minimal and measured quantity of 5% sodium citrate compared favorably with those of macromethods. Westergren⁸ pointed out that the sedimentation rate with 3.8% sodium citrate used in his test differed to a slight degree only from that with the 5% solution.

The sedimentation test with the use of finger blood, described by Cutler,² involved the use of a pipette whose bore and stem dimensions were similar to those of the tube employed in this study. A primary difficulty with the Cutler micromethod, however, rose from its dependence upon traces of sodium citrate solution adhering to the walls of a small storage tube to prevent the blood from clotting. In addition, considerable technical skill and dexterity were required in order to retain the measured specimen within the stem of the pipette until a spring attachment could be applied in order to seal off the bottom.

A special pipette (Fig. 1a) was, therefore, designed for drawing up capillary blood similar to the one employed for hemoglobin determinations by the Sahli method. Two graduations are present, one at 0.04 cc., the other at 0.1 cc., the latter representing the total calibrated capacity of

* The complete apparatus required for the test may be obtained from E. Machlett & Son, 220 East 23rd Street, New York City.

the pipette. The pipette is sufficiently long so that capillarity is maintained within it. This feature is of particular importance so that blood already withdrawn is not lost in the event of sudden movement of the child.

The first step in the procedure is to moisten the inside of the entire pipette by drawing 5% sodium citrate throughout its length several times and eventually discarding all but 0.04 cc., which is the first graduation on

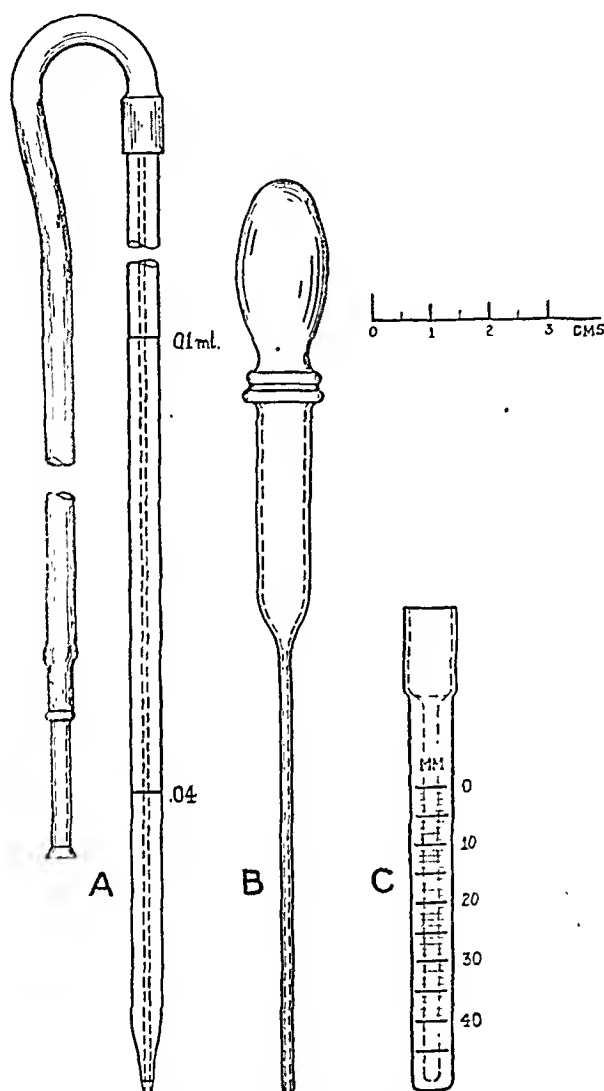


FIG. 1.—A, Pipette for measuring the citrate solution and for collecting blood; B, pipette with bulb for transferring citrated blood to, C, sedimentation tube.

the pipette. The latter quantity is expelled into the bottom of an ordinary test tube and is sufficient to prevent the coagulation of 0.3 cc. of blood. Blood for the test is obtained by puncture of the finger tip of the child, or of the heel in the instance of the young infant. The puncture site is carefully prepared and a sharp needle is used, or preferably, an automatic lancet, since the latter secures a free flow of blood which is an essential prerequisite for accuracy of the test. Moderate pressure of the finger tip or heel in order to secure a complete specimen did not interfere with the test.

Blood is withdrawn (0.3 cc.) by 3 consecutive aspirations of 0.1 cc. with the pipette, using rubber tubing for suction as for a blood count. As each 0.1 cc. of blood is collected, it is transferred to the test tube and shaken vigorously to secure thorough admixture with the sodium citrate solution. Following the expulsion of the second 0.1 cc. some of the citrated blood is sucked up the pipette throughout its length and then returned to the test tube. After the addition of the final 0.1-cc. fraction of blood, the tube is corked, and the contents are thoroughly admixed once more. The test may be performed at once or may be postponed for several hours. Should the specimen clot within the test tube, it is due to inadequate finger puncture, the preliminary introduction of less than 0.04 cc. of citrate solution, or to failure to agitate the blood thoroughly so as to secure complete interaction with the anticoagulant.

The citrated blood is transferred to the sedimentation tube by means of a simple capillary or Wright pipette with an attached rubber bulb (Fig. 1b). This type of pipette is readily prepared in the office or laboratory from ordinary soft glass tubing, and is of sufficient width to receive the small rubber bulb in common use. The capillary portion must be adequate to reach the bottom of the sedimentation tube. The latter is filled by the gradual release of the citrated blood by gentle pressure on the bulb as the pipette is slowly withdrawn from the bottom of the tube until the uppermost "0" mark is reached. Any excess above this graduation is easily removed with the same pipette. The tube is placed in a rack and the rate of sedimentation is recorded. All tests were carried out at room temperature.

The time at which the readings are made vary with many observers. The "corrected sedimentation index" of Rourke and Ernste,⁹ which incorporates the most desirable refinements of the technique, requires the measurement of the rate during the phase of most constant sedimentation, distinct from the preliminary period of erythrocytic aggregation and the final one of packing. This method necessitates readings at periodic intervals, the plotting of a curve and subsequent correction for anemia. With the Cutler graphic technique³ the level of the sedimenting column is recorded at 5-minute intervals for 1 hour. From these determinations, 4 types of graphs are constructed, each corresponding to a different degree of cellular destruction accompanying infection.

In order to simplify the test and to render it suitable for routine clinical use, the plan adopted in this study was to record the level of the upper layer of the sedimenting erythrocytes at the end of $\frac{1}{2}$ hour and 1 hour. The two readings furnish an approximate idea of the velocity with which the red cells settle, although practically and for comparative purposes the single observation after 1 hour was sufficient.

Cleaning the tube was readily accomplished with the capillary pipette previously employed for transferring the citrated blood from the storage test tube to the sedimentation tube. Water was forced through to the bottom of the sedimentation tube several times by firm pressure on the bulb of the pipette until the return flow was clear. Alcohol and ether in turn were introduced and the tube was removed by forcible shaking.

In order to determine the efficiency of the microsedimentation tube described in this paper, comparison was made with a standard method using venous blood. The Cutler technique was chosen because of the similarity in the height and subdivisions of the graduated portion of both tubes.

Comparative tests (102) were carried out with the blood of 84 infants and children ranging in age from 12 days to 14 years, of whom 43 were sick and 41 healthy. For the macromethod 0.1 cc. of 3% sodium citrate solution and 0.9 cc. of blood obtained by veni-

puncture were mixed and expelled from the syringe into a Cutler tube of 1-cc. capacity graduated into 50-mm. divisions. In 95 instances, comparative tests with Cutler and microsedimentation

TABLE 1.—COMPARISON OF SEDIMENTATION RATES WITH CAPILLARY AND VENOUS BLOOD IN NORMAL INFANTS AND CHILDREN.

Case No.	Patient.	Age.		Date.	Sedimentation rate.				Cell volume percentage anticoagulant.	
		Yr.	Mo.		Venous blood, Cutler method.		Capillary blood, author's blood.		Heparin, %	5% sodium citrate, %
					30 min., mm.	1 hr., mm.	30 min., mm.	1 hr., mm.		
1	K. A.	8	.	4/ 9/35	2	7	2	8	45	37
2	J. B.	3	6	11/ 1/34	6	11.5	6	12	42	34
3	B. B.	7	.	2/19/35	2.5	6	3	7	42	36
4	H. B.	.	5	2/22/35	2.5	7	2.5	6	45.5	42
5	R. B.	4	.	5/21/35	6	12	6	12	43	36
6	G. C.	7	.	10/ 9/34	6	10.0	7.5	12	45	40
7	X. C.	12	.	3/21/35	2	6	3	6	42.5	36
8	W. E.	.	11	2/11/35	4	10	4	10	41.5	32
		.		2/16/35	5	9	5	10	42	35
9	M. F.	5	.	12/ 2/34	5	8	5.5	9	44	35
10	T. F.	4	.	10/25/34	4	8	6	11	43	39
11	J. F.	.	13	3/ 7/35	7	12	6	12	44	35
12	F. F.	8	.	2/14/35	5	10	6	11	44	38
13	E. F.	10	6	10/30/34	3	8	6	10.5	45.5	40
14	M. G.	2	10	3/ 9/35	3	7	3	8	42.5	36
15	H. G.	6	.	11/20/34	5	11	7	12	40	33
16	I. H.	11	6	1/27/35	3	9.5	4	10	43	39
				2/ 5/35	4	7	4	8	43	36
17	E. H.	6*	.	12/14/34	5	11	5	11	37.5	34
18	M. H.	.	15	12/20/34	4	9	2	10	37.5	31
19	R. H.	2	.	11/ 5/34	1.5	6.5	1.5	6.5	43	36
20	K. K.	10	6	4/30/35	2	6	2	6	44.5	39
21	A. L.	9	.	10/11/34	2	8	2	9	44	36
22	W. MacI.	5	8	2/ 7/35	2	5	1.5	4	42	36
23	D. M.	7	.	6/20/35	6	12	7	13	41	32
24	A. M.	12	.	3/20/35	1	3	1	3	46.5	38
25	A. N.	9	.	2/23/35	2	6	2	6	43.5	36
26	J. McQ.	11	6	10/13/34	2	6	2.5	6	42	35
27	R. M.	2	.	1/ 7/35	7	12	7	12	38	32
28	G. M.	14	.	6/ 8/35	3	10	4	12	41	34
29	F. M.	.	17	5/14/35	5	10	5	11	40	31
30	R. P.	.	22	3/12/35	5	9.5	5	10	42	34
31	B. P.	12†	.	1/16/35	4	10	2.5	6	58	50
32	T. R.	6*	.	2/21/35	4	7	4	7	51	44
33	F. R.	11	6	1/29/35	4	9	6.5	10	47	38
34	G. R.	9	.	11/13/34	1	4	1	3	47	38
35	M. R.	12	.	5/23/35	4	7	5	8	42	37
36	G. R.	11	.	4/ 6/35	4	8	3	7	44	37
37	J. R.	10	.	6/22/35	8	13	8	13	41	35
38	H. S.	8	.	12/ 1/34	4	9	7	11	44.5	36.5
39	F. S.	9	.	2/19/35	7	11	4	11	47	38
40	R. T.	8	.	11/27/34	2	8.5	5	10	42	34
				12/ 4/34	4.5	9	4	10	44	36
41	J. V.	.	3	1/28/35	2	7	4	9	43	34
42	R. Z.	.	7	10/10/34	4	10.5	5	11	36	30

* Weeks.

† Days.

tubes were carried out in which heparin* was substituted for sodium citrate solutions. In addition, 128 microsedimentation tests were carried out without comparison with the macromethod, except that

* A solution of heparin was prepared by dissolving 50 mg. in 2 cc. of distilled water. One drop dried in a test tube was sufficient for inhibiting coagulation of at least 0.3 cc. of capillary blood for the microsedimentation test, and 3 drops for 1 cc. of venous blood for the Cutler tube.

a duplicate microsedimentation test was performed with heparin as an anticoagulant.

The purpose of the tests with heparin was to compare the sedimentation rates as well as cell volume percentages after centrifuging, with values for citrated blood. Since heparin as anticoagulant does not hasten or retard the sedimentation rate as occurs with the sodium citrate and the other salt anticoagulants,⁷ the results were of value from a comparative standpoint. At the termination of each sedi-

TABLE 2.—SUMMARY OF RESULTS COMPARING SEDIMENTATION RATES BY CAPILLARY AND VENOUS BLOOD METHODS.

Method.	No. cases.	No. tests.	Sources of blood.	Anticoagulant.	Sedimentation rate.			
					30 min., mm.		1 hr., mm.	
					Average.	Extremes.	Average.	Extremes.
1. Normal Group.								
Microsedimentation	42	45	Finger*	5% sodium citrate	4.3	1-8	9.1	3-13
Cutler	42	45	Vein	3% sodium citrate	3.9	1-8	8.6	4-13
Microsedimentation	38	40	Finger	Heparin	5.5	1-13	12.0	3-21
Cutler	38	40	Vein	Heparin	4.7	0-13	10.1	3-21
Summary of microsedimentation tests†	60	72	4.2	1-8	9.1	3-13
2. Pathologic Group.								
Microsedimentation	43	57	Finger	5% sodium citrate	15.1	3-33	20.8	8-35
Cutler	43	57	Vein	3% sodium citrate	14.6	3-34	20.6	8-35
Microsedimentation	43	55	Finger	Heparin	15.2	3-32	22.2	11-33
Cutler	43	55	Vein	Heparin	15.8	1.5-32	22.2	9-33

* Blood was obtained from the heel in very young infants.

† These tests were performed according to the technique described in the text with the use of capillary blood after treatment with 5% sodium citrate.

mentation test the tubes with heparinized and citrated blood were centrifuged at a speed of 2500 revolutions per minute for 30 minutes. The number of millimeters of packed cells multiplied by 2 constituted the cell volume percentage. The latter values with heparin were on the average 7.5% higher than with sodium citrate (Table 3), due to the fact that the former expresses the results with whole blood whereas the latter is derived from that of a diluted specimen (0.4 to 0.3 cc. of blood). Furthermore, the erythrocytes undergo shrinkage with sodium citrate and other inorganic salts as contrasted with heparin which does not affect them.

A total of 240 microsedimentation tests were performed with sodium citrate as anticoagulant. Wherever possible, also, hemoglobin and red cell determinations were carried out simultaneously with the sedimentation tests.

Results. In Tables 1 and 2 the readings at $\frac{1}{2}$ - and 1-hour periods are presented. The close correspondence in the results with the capillary and venous blood is at once apparent. As noted, in 45 tests with the blood of normal children ranging in age from

12 days to 14 years, the average sedimentation rate at the end of $\frac{1}{2}$ hour was 4.3 mm. with the micromethod and 3.9 mm. with the macromethod. At the end of 1 hour the rate was 9.1 mm. with the former and 8.6 mm. with the latter. The 1-hour values fell within the range usually stated for the Cutler venipuncture method for normal adults. When the results of 27 additional microsedimentation tests with the blood of normal children were averaged with the 45 tests already noted, the rate for the finger-blood method for $\frac{1}{2}$ hour was 4.2 mm. and for 1 hour 9.1 mm., with respective ranges of 1 to 8 mm. and 3 to 13 mm.

In 57 tests of the pathologic group with children of a similar age distribution, the average reading for the $\frac{1}{2}$ -hour period was 15.1 mm. with the micromethod as compared with 14.6 mm. with the macromethod. At the end of 1 hour the sedimentation rate with the former method was 20.8 mm. as compared with 20.6 mm. for the latter. The rates were slightly more rapid with the use of the microtube. It is significant, however that the differences were slight. The tendency of the 5% sodium citrate solution acting as an anticoagulant for finger blood to produce a slightly slower sedimentation rate than that with the weaker solution used for venous blood is counteracted by the more rapid settling of erythrocytes that occurs within the narrower microtube than in the wider Cutler tube.

Van Antwerp's observation¹⁰ that successive sedimentation tests in children were subject to wide variations without apparent cause was not borne out in the present study. It will be noted in Table 1 that in the 3 children with whose blood, tests were repeated at intervals ranging from 5 to 9 days, the rates obtained were almost identical. In 8 additional instances with the blood of normal children not included in this table, successive microsedimentation tests, carried out over a period from 2 days to 2 months revealed a maximum difference at the end of 30 minutes and 1 hour of 3 mm., this usually following the longest time intervals. In 26 determinations with the blood of sick children, repetition of the test within a period of a week, yielded surprisingly similar results unless the condition had undergone obvious clinical alteration. In this group the average difference in rates obtained in successive tests was less than 2 mm. in $\frac{1}{2}$ hour and less than 1 mm. in 1 hour, the most uniform results being observed at the latter reading. In many instances duplicate estimations were carried out with successive specimens of blood from the same finger prick, with resulting readings that varied within a fraction of a millimeter. The discrepancies noted by Van Antwerp may possibly be accounted for by variations in the cell volume in repeated determinations or by changes in the status of the patient not in evidence clinically. Exact agreement between sedimentation rates even in the normal individual over intervals of 24 hours or more cannot always be expected. While progressive cellular destruction is expressed in

the wider fluctuations with which erythrocytes settle out of plasma, minor variations may reflect subtler aberrations in the ordinary physiologic mechanisms.

The close agreement in the rates of consecutive estimations emphasizes the reliability of the microsedimentation tests described in this study. In Table 2 a summary of the comparative sedimentation tests are presented in which the influence of heparin and sodium citrate are contrasted. The more rapid settling that occurs with heparin confirms the observations of Rourke and Plass,⁷ who found that this substance does not affect the sedimentation of erythrocytes, whereas solutions of the inorganic anticoagulants serve to slow the reaction. For the relatively short tubes employed in this study, sodium citrate is preferable to heparin, since the greater distances traversed by the red cells of blood treated with the latter substance cause confusion at times in the interpretation of results in the case of normal individuals. Heparin constitutes an ideal anticoagulant, however, for use with longer sedimentation tubes where the larger sedimented layers are more readily comparable.

A fundamental consideration in the evaluation of the test is the influence of the concentration of hemoglobin, erythrocytes and the cell volume percentage of the latter upon the sedimentation rate. That an inverse ratio exists between the rate of settling of the cells and their number has been pointed out by many investigators. The more rapid rate of settling in a blood with fewer red cells is exemplified in instances of individuals with anemia whose sedimentation rates are comparable to those of patients with severe infections but who possess a normal complement of erythrocytes. Since the test was designed to indicate the degree of existing infection and tissue damage, attention has been directed toward means of correcting the sedimentation rate for fluctuations in the content of erythrocytes. The many procedures that have been proposed have for their purpose the transposition of the final sedimentation rate in terms of blood containing either a normal number⁵ or a normal volume percentage of erythrocytes.^{6,9}

The methods range from a preliminary adjustment of the blood sample so as to obtain a red cell count of 5,000,000 per c.mm.,³ to the correction with the aid of a chart for a normal cell volume after recording the rate of settling during short intervals so as to determine the period at which it takes place most rapidly.⁹ Wintrobe and Landsberg's method⁶ is simplified in that a single reading at the end of 1 hour is corrected for a normal volume of packed red cells.

While it is doubtless true that the correction for the concentration and volume percentage of erythrocytes is justified because it eliminates an important factor leading to equivocal interpretation, nevertheless objections have been raised at attempts for refinements

of the test. In the first place, a moderate reduction of the red cells is a frequent accompaniment of most infectious processes. Since these two factors move in close association throughout the course of an illness, it has been emphasized¹¹ that the uncorrected sedimentation rate constitutes an accurate index of the stage of pathologic activity and clinical status of the patient. This is true in the majority of instances, although it is not uncommon for the anemia to outrun the infection.

In addition, methods for correction are usually not interchangeable because of the lack of uniformity of sedimentation tubes, anti-coagulants and technique. Wintrobe and Landsberg,⁶ for example, showed that sedimentation proceeded more rapidly in a longer tube than in the shorter one. Thus, the red cells settle more rapidly in the 100-mm. tubes employed by Rourke and Ernstene,⁹ and Wintrobe⁴ than in the 50-mm. Cutler tube or in the one described in this paper. It is usually necessary, therefore, to determine a method for correction adapted for each type of test. Hubbard and Geiger¹² have also pointed out the difficulty of establishing an average normal sedimentation rate to serve as a basis for comparison because of the differences that exist in the speed of settling in blood specimens whose cellular constituents are numerically identical. The test, furthermore, finds its greatest usefulness not in the information derived from a single determination but by periodic repetition when it serves as a guide to the progress of infection. Fluctuations in erythrocytic content during short intervals are usually not sufficiently pronounced to alter the sedimentation rate as are the changes in the pathologic condition. Because of these considerations, many writers maintain that the sedimentation test serves its best purpose as a laboratory procedure simple of performance, and that correction only limits its availability for routine clinical use.

The drawback of introducing refinements which complicate the test cannot be denied. As a practical measure, however, it would seem best to carry out the test according to a prescribed method, but whenever possible to take cognizance of the erythrocyte content of the blood, especially where the rate departs markedly from the normal. This information may be obtained by determining the red cell count or the relative cell volume of the blood at the time of the test. Of the two, the estimation of the cell volume percentage is more significant, since this constitutes a combined measurement of the number of cells together with their size.

In the course of this investigation, it appeared important to compare the cell volume percentages in the normal with those of the pathologic group at the time of the sedimentation tests. The object was to observe to what extent anemia was associated with infection. The pathologic conditions were the common ones occurring in children and included in the main rheumatic disease, pneumonia,

childhood tuberculosis and upper respiratory infections. Blood dyscrasias were excluded.

As already stated, sedimentation tests were carried out not alone with 5% sodium citrate solution recommended for the microsedimentation tube described in this study, but also with heparin as anticoagulant. The reason for the higher volume percentage of packed cells with heparinized blood than with the sample treated with citrate has already been discussed. It may be noted in Table 3 that the packed cell volume in the group of normal children ranged from 36 to 49% in the heparinized blood and from 30 to 40% in the citrated blood. In the pathologic group the limits were 31.5 to 48% with heparinized blood and 26 to 42% with the citrated blood. In the pathologic group a hematocrit value of 36% and

TABLE 3.—SUMMARY OF CELL VOLUME PERCENTAGES.

Age.	No. cases.	No. tests.	Anticoagulant.			
			Heparin, %.		5% sodium citrate, %.	
			Average.	Extremes.	Average.	Extremes.
1. <i>Normal Group.</i> 11 mos.*-14 yrs.	54	68	43	36.0-49	35.8	30-40
2. <i>Pathologic Group.</i> 11 mos.*-13½ yrs.	66	162	41	31.5-48	33.5	26-42

* The observations below this age level were few in number and were omitted to facilitate comparison between the two groups.

over (lower level of the normal group) occurred in 93.8% of the heparinized blood specimens, and a value of 30% and over (lower level of the normal group) in 95% of the citrated bloods. It appears, therefore, that in the small unselected group of children with a variety of disease conditions, the erythrocytic concentrations as judged by the cell volume fell in the majority of instances within the range observed in the comparable normal group. Of course, the extremes for each group are subject to the modifications of larger series of cases and with the inclusion of more prolonged and a greater variety of infections.

The diversity of normal standards for cell volume percentages reported in the literature has added to the difficulty of designating an arbitrary value in terms of which correction is to be effected. The differences arise from the use of anticoagulants that cause changes in the osmotic pressure of the blood, the element of dilution, and the variation of the time and speed of centrifugation. In a recent investigation, for example, Osgood and Baker²³ found with the use of oxalated venous blood that the cell volume percentage in 215 tests in normal children, between the ages of 4 and 13 years, ranged between 28.76 to 46.51%, with an average of 36 cc. of packed cells

per 100 cc. of blood. With their method a correction of 3.5% of the volume of packed cells was necessary because of shrinkage due to the use of oxalate as anticoagulant. Centrifugation was carried out by them at over 4500 revolutions per minute,¹⁴ until the cell volume remained constant. From the normal group reported in the present study, 43.5 cc. was the average cell volume per 100 cc. of blood of 51 tests in children of a similar age group. This value was obtained with heparinized blood after the specimens were centrifuged at an average time and speed of 30 minutes at 2500 revolutions per minute. Since heparin does not disturb the osmotic relations of the blood, no correction for shrinkage was necessary. This value corresponds to the hematocrit reading of 43.7 cc. of packed red cells per 100 cc. of blood for adults obtained by Haden¹⁵ with the use of an isotonic solution of sodium oxalate.

Millar¹⁶ and Ponder and Saslow,¹⁷ in appraising the hematocrit method as a means of cell volume measurement questioned its accuracy because of the difficulty of deciding upon the end point. The hematocrit remains, however, the most practical instrument available for this type of determination and is thoroughly reliable for comparative purposes provided the technique is unchanged. Although the complete removal of fluid between the erythrocytes is desirable, it is possible that in obtaining this objective, changes may be induced by compressive forces upon the blood of individuals of various age groups especially when coagulation is inhibited through the medium of substances that induce shrinkage. Haden¹⁸ found that at a speed of 2500 revolutions per minute the volume of cells after $\frac{1}{2}$ hour centrifugation was only 2% greater than after 2 hours. The time and speed of centrifugation followed in the present study yielded results that differed to a slight degree only with those at higher speeds. In a small series of comparative estimations the cell volume with heparinized and citrated blood obtained after centrifuging at the standard speed of 2500 revolutions per minute for $\frac{1}{2}$ hour exceeded by only 1% as a maximum the values obtained after centrifuging at a speed of 4000 revolutions per minute for $\frac{1}{2}$ hour to 45 minutes. Because of the possibility of undesirable alterations with the blood of young individuals, the lower speed was adhered to.

In conclusion, it may be stated that the significance of an isolated, uncorrected sedimentation rate of a patient with an infection taken apart from a series, increases when the cell volume percentage falls within the range of normal, and that it may be accepted without reservation when it approximates the average figure. With the method described in this paper, and until larger series of observations are reported, the lower level of cell volume for citrated blood specimens may be regarded as 30% and the average as 36%. Comparison with these values is only essential when marked deviations from the normal rate of settling are noted in an initial test or with the occurrence of a sudden and unexpected shift in the course of

consecutive tests. Where facilities are available for centrifugation at the requisite speed, however, it would be desirable to determine and record the cell volume percentage together with the sedimentation rate. Such conjoint measurements are helpful in the final evaluation of the test, and when obtained periodically provide useful information in regard to the clinical and hematologic progress of the patient.

Summary. A method of determining the sedimentation rate of erythrocytes has been presented which employs capillary blood and is suitable for use with infants and children.

The tube that has been devised constitutes in effect a reduced macrosedimentation tube in that it embodies the basic requirements of apparatus in which sedimentation tests are carried out with venous blood.

Close agreement was noted in 102 comparative determinations with the method, in addition to 128 other microsedimentation tests, using blood from the heel of the young infant or finger of the older child and with a standard test utilizing venous blood.

With the microsedimentation method described in this study in which 5% sodium citrate was employed as anticoagulant, the average rate of settling in normal infants and children was 4.2 mm. for $\frac{1}{2}$ -hour and 9.1 mm. for 1 hour, with respective ranges of 1 to 8 mm. and 3 to 13 mm. The single determination at the end of 1 hour was sufficient for comparative purposes.

At the conclusion of the sedimentation test, the tubes were centrifuged for $\frac{1}{2}$ hour at a speed of 2500 revolutions per minute. The range of cell volume in the normal group was 30 to 40% for citrated blood (average, 35.8%).

In a small group of infants and children with various infections, 95% showed cell volumes of 30% for citrated blood (lower level of the normal group) and over. This minimal value is tentative and may require modification with more extensive investigation.

Since the determination of the sedimentation rate has been applied chiefly as a guide to infection, various procedures have been devised to correct for the factor of anemia which in itself markedly influences the rate. While these methods are valuable, they are subject to the criticism that the test is thereby complicated and its availability for routine clinical use limited. It has, furthermore, been emphasized that moderate grades of anemia cannot be dissociated from infection and that they usually fluctuate together.

In the light of these objections and of others that are discussed, it is suggested that wherever possible the cell volume percentage be reported together with the sedimentation rate. The rate of settling may then be evaluated in accordance with the extent to which the cell volume percentage approximates the range of normal, instead of substituting for it a value derived by comparison with an arbitrary standard.

Since this paper was submitted for publication a large number of micro-sedimentation tests have been carried out and on the basis of this additional experience several technical details require reiteration. In the first place, the finger puncture must be adequate to insure a free flow of blood so that the complete specimen may be quickly obtained. Secondly, sufficient anticoagulant must be employed to prevent clotting of the blood from all types of pathologic conditions. To make certain of this, thorough preliminary rinsing of the pipette with the 5% sodium citrate should be effected and care should be exercised to introduce at least 0.04 cc. of this solution into the collecting test tube. If the column of anticoagulant falls below the 0.04 cc. graduation, clotting may occur, whereas, if this amount is slightly exceeded, the sedimentation rate is not perceptibly influenced.

As an extension of the studies described in this paper, cell volumes were determined, using the microtube as a hematocrit in which the results with a mixture of oxalates (Heller, V. G., and Paul, H.: *Changes in Cell Volume Produced by Varying Concentrations of Different Anticoagulants*, *J. Lab. and Clin. Med.*, 19, 777, 1934) were compared with those using heparin. An oxalate solution of 0.04 cc. (1.5 gm. of ammonium oxalate and 1 gm. of potassium oxalate dissolved in 100 cc. of water) was drawn up in the pipette, expelled into a collecting test tube and allowed to dry. This was sufficient to prevent clotting of 0.3 to 0.4 cc. of finger blood. The volume of packed red cells obtained after centrifuging the oxalated blood closely approximated the values obtained with the heparinized blood and were usually identical. The sedimentation of red cells from the oxalated blood in the microtube, however, did not proceed as smoothly and with the same regularity as did heparinized or citrated blood. The microsedimentation tube may, therefore, be employed as a reliable hematocrit for determining the actual volume percentage of red cells with the substitution for heparin of the less expensive and more available mixture of oxalates.

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MACROCYTIC ANEMIA IN LIVER DISEASE, PARTICULARLY CIRRHOSIS.

OBSERVATIONS ON THE INCIDENCE, COURSE AND RETICULOCYTOSIS, WITH A CORRELATED STUDY OF THE GASTRIC ACIDITY*

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IN recent years, reports of the occurrence of macrocytosis or of macrocytic anemia in diseases of the liver, unassociated with hemorrhage, have appeared in the literature with increasing frequency. Prior to this, the finding of this characteristic of pernicious anemia, particularly in hepatic cirrhosis, was regarded as most unusual,¹ meriting brief if any comment in treatises on this subject, all emphasis being laid upon the anemia secondary to hemorrhage.

The earliest observation of the coexistence of macrocytosis with liver disease was made in 1883 by Gram,² who found the diameter of the erythrocyte increased in obstructive jaundice, catarrhal jaundice and in a case of cirrhosis. Limbeck³ (1896) found the volume of the red cells increased in catarrhal jaundice, and Capps⁴ (1903) observed a high volume index in 2 cases of carcinoma of the liver. Recently, Wintrobe and Shumacker⁵ recorded 11 instances of macrocytosis, and collected from the literature 57 other cases of macrocytic anemia associated with different forms of cirrhosis. To their series, I am able to add at least 80 cases of liver disease with macrocytosis found in a subsequent survey of the literature.^{2,3,4,6-20} As with rare exceptions,^{5,6} the reports deal with single cases or with small groups, an investigation of the incidence, nature and course of these morphologic changes in a larger series of patients with liver disease was undertaken, a report of which constitutes the basis of this paper.

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Material. Observations were made upon 62 cases of acute, subacute and chronic hepatic disease, 48 of which were cirrhosis, 7 toxic hepatitis, 1 acute yellow atrophy, 3 carcinoma of the head of the pancreas and 3 metastatic carcinoma of the liver. In the selection of patients, only those in whom a diagnosis of liver disease could be made without equivocation were chosen. The necessity for adhering to such a rigid criterion is borne out by the paucity of necropsies and operations performed in this group, only 10 in all. In consequence, the majority of the cases represent advanced hepatic disease.

A few brief remarks about the clinical features of the cases of cirrhosis may assist in visualizing the type and extent of the disease: Of 45 patients diagnosed as portal cirrhosis, 41 were in the hypertrophic and 4 in the atrophic stage. In 3 other patients, hypertrophic biliary cirrhosis was found at operation. The liver edge in the hypertrophic group was distinctly hard, and averaged 8.1 cm. below the costal margin on inspiration, with the limits of variation being 2 to 14 cm. In 31 cases, the surface was smooth, and in the remaining 13, it was irregular and nodular. The spleen was slightly to moderately enlarged in 11 patients, and in another, it descended 7 cm. below the costal margin. Ascites was present in 31 individuals, and edema of the lower extremities in 22. A history of chronic alcoholism was elicited in 31 of the patients, and 9 of these presented the manifestations of delirium tremens either upon entry or while in the hospital. Of the 62 patients studied, intrahepatic jaundice of a greater or lesser degree, indicating considerable hepatic dysfunction, was observed in 40 instances (Tables 1, 2, 3 and 4).

Methods. Blood counts were made every 3 or 4 days during the period of hospitalization and at variable intervals thereafter. Counting chambers and pipettes certified by the U. S. Bureau of Standards were used, and hemoglobin estimations were made with a Sahli hemometer standardized so that 14.5 gm. was equivalent to 100% (Wintrobe).²¹ Cell volumes were determined by the Wintrobe hematocrit.²¹ To obviate any possibility of congestion in the forearm, the tourniquet was released immediately after insertion of the needle into the vein, and a few seconds were allowed to elapse prior to withdrawal of the blood. Reticulocyte counts were made from blood supravitaly stained with brilliant cresyl blue. Wherever indicated, fragility tests were made in order to aid in differentiating acquired or familial hemolytic icterus. In all cases, the degree of bilirubinemia was measured by the icterus index.²² To study the relationship, if any, between achlorhydria and this type of anemia, Ewald test meals were given wherever feasible, and to patients showing an acidity by this method, 0.35 mg. of histamin was administered subcutaneously and a fractional gastric analysis was performed.

Results. *Hepatic Cirrhosis.* Of the 48 patients with cirrhosis (Tables 1 and 2), a macrocytosis was found in 43 instances, an incidence of 89.7%*. This is strikingly shown by the mean corpuscular volume, which ranged from 75.4 to 142.5 c. μ ., the average being 110.8 c. μ . The extraordinarily high figure of 142.5 c. μ . was obtained in Patient 18, at a time when the reticulocytes numbered 18% of the total red blood cells, and, from the work of Persons,²³

* Dr. A. C. Ivy, Professor of Physiology at Northwestern University, has written us in this regard. "Dr. Rosenberg, as well as I, was surprised in regard to the high incidences of macrocytosis observed. When this appeared to be true during the earlier stages of his work, his technique was investigated for faults, and none found. It was then thought that as the work progressed the percentage would decrease; but it did not."—EDITORS.

TABLE 1.—HYPERTROPHIC CIRRHOSIS.

Patient.	Age.	Duration of Symptoms.	Hb.	R.B.C.	Vol.* R.B.C.	C. V.*	C. H.*	C. H. C.*	Reticulo-cytes.	Icterus Index.	Acidity.
			gm. per 100 cc.	millions per c.mm.	cc. per 100 cc.	c. μ	$\mu\mu$	per cent.	per cent.		
1	45	2 yrs.	7.8	2.35	25.0	106.4	33.2	31.2	1.9	38	+
2	62	1½ yrs.	10.3	3.01	31.2	103.7	34.2	33.0	0.7	25	0
3	50	6 mos.	8.0	1.67	22.2	133.0	46.0	36.0	1.7	58	0
4	45	6 yrs.	13.6	3.78	42.5	112.6	36.0	32.0	0.1	140	0
5	35	3 yrs.	13.1	3.75	45.4	121.0	34.8	28.7	0.2	6	0
6	49	4 mos.	10.4	3.13	37.0	118.0	33.4	28.2	1.5	50	+
7	54	6 mos.	13.2	3.95	40.7	102.4	33.2	32.4	0.1	6	0
8	52	5 mos.	10.0	2.69	29.6	110.0	37.0	34.0	1.6	20	0
9	50	10 mos.	2/5/35 11.2	3.83	23	0
			2/13/35 13.0	3.96	47.4	120.6	32.8	27.4	0.7		
			2/20/35 13.4	3.95							
10	52	4 yrs.	13.2	3.24	37.7	116.0	40.7	35.0	3.8	33	0
11	43	16 yrs.	1/10/35 11.2	4.05	4	0
			2/15/35 14.5	4.21	52.6	125.0	34.4	27.6	1.8		
			5/1/35 14.5	5.26	53.0	100.8	27.6	27.4			
			7/12/35 15.2	4.49	47.4	105.6	33.9	32.1	1.5		
12	40	6 mos.	12/6/34 10.9	3.99	1.7	22	
			2/15/35 13.0	4.01	43.8	109.0	32.4	29.7	
			3/15/35 14.0	4.31	44.3	102.9	32.5	31.6	0.5		
			7/12/35 15.0	4.13	44.1	106.8	36.3	34.0	0.6		
13	47	8 yrs.	14.0	3.23	38.8	120.0	43.4	36.1	0.2	66	0
14	48	3 yrs.	12.4	3.89	42.8	110.0	31.9	29.0	0.8	4	0
15	42	2 mos.	3/15/35 13.8	3.75	42.4	113.0	36.8	32.5	0.9	6	0
			5/10/35 14.6	4.23	46.3	109.6	34.6	31.5			
16	50	2 mos.	12.8	3.14	35.8	114.4	42.4	35.8	0.8	34	+
17	34	1 mo.	9.5	3.24	31.0	104.8	29.3	28.0	3.5	25	0
18	39	1 yr.	2/13/35 12.4	2.66	32.5	122.0	46.6	38.1	2.6	115	0
			3/13/35 5.2	1.09	15.5	142.5	47.8	33.5	18.0	60	
19	63	3 yrs.	3/13/35 12.6	4.42	42.9	96.9	28.5	29.4	0.0	6	
			5/22/35 12.8	4.27	41.2	96.4	29.9	31.1	1.3		
			7/ 3/35 14.0	3.98	43.7	109.8	35.2	32.0	1.0		
20	38	5 mos.	11.8	4.07	34.5	84.7	29.0	34.2	1.3	28	0
21	34	6 yrs.	13.1	3.30	40.3	122.0	39.4	32.2	2.1	34	0
22	52	3 wks.	13.0	3.56	39.0	109.7	36.6	33.3	1.8	30	
23	44	?	11.4	3.10	35.7	115.2	36.8	32.0	3.0	6	0
24	47	4 yrs.	12.6	3.31	34.0	102.7	38.1	37.1	2.3	28	0
25	31	1 yr.	9.6	3.53	30.0	85.0	27.2	32.0	1.2	26	
26	45	1 yr.	13.2	4.97	40.0	80.4	26.5	33.0	1.9	4	
27	43	1 yr.	16.2	4.14	52.1	126.0	39.2	31.1	0.2	3	0
28	42	7 yrs.	11.2	2.18	25.1	123.6	51.3	39.9	7.0	60	0
29	44	6 mos.	8.4	3.28	24.7	75.4	25.6	34.0	2.4	24	0
30	43	2 mos.	9.8	2.39	25.3	118.6	41.0	34.6	5.3	91	
31	46	?	16.4	4.41	50.5	114.5	37.2	32.5	0.6	4	
32	60	2 mos.	5/22/35 14.2	4.21	39.1	92.8	33.7	36.3	0.6	26	0
			6/21/35 13.0	3.76	39.1	104.0	34.6	33.2	1.3		
33	38	7 mos.	12.6	3.30	36.0	109.1	38.2	35.0	2.6	5	+
34	43	2 wks.	9.4	2.48	28.3	114.0	37.8	33.2	2.1	26	+
35	50	3 mos.	12.6	3.71	36.5	98.4	34.0	34.5	1.1	9	+
36	52	3 wks.	13.4	2.96	36.5	123.2	45.2	36.7	1.8	18	+
37	46	?	11.8	3.88	37.8	97.5	30.5	31.5	0.7	7	0
38	26	3 mos.	13.2	3.59	36.2	101.0	36.8	36.5	1.4	4	0
39	36	2 mos.	8.0	1.55	23.9	136.6	45.7	33.5	3.1	22	0
40	43	2 mos.	11.4	3.41	37.8	110.8	33.4	39.2	0.9	6	+
41	58	3 mos.	13.4	2.78	33.0	115.9	49.3	40.6	0.4	155	0
42	40	6 mos.	10.4	2.02	26.4	130.4	51.4	39.4	1.3	90	+
43	47	?	14.4	3.63	40.8	112.4	39.7	35.3	3.2	90	
44	54	3 wks.	10.2	2.73	30.7	112.2	37.1	33.2	4.3	18	0

* Vol. R.B.C.—Volume of packed red blood cells in 100 cc. of blood.

C. V.—Mean corpuscular volume in cubic microns. Normal, 80 to 94 c. μ .C. H.—Mean corpuscular hemoglobin in micromicrograms. Normal, 27 to 32 $\mu\mu$.

C. H. C.—Mean corpuscular hemoglobin concentration in per cent. Normal, 33 to 38%.

Only significant changes noted during the period of observation are recorded in the tables.

TABLE 2.—ATROPHIC PORTAL CIRRHOSIS.

Patient.	Age.	Duration of symptoms	Hb.	R.B.C.	Vol., R.B.C.	C. V.	C. H.	C. H. C.	Reticulo-cytes.	Icterus index.	Anacidity.
			gm. per 100 cc.	millions per c.mm.	c.c. per 100 cc.	c. μ .	$\mu\mu$	per cent.	per cent.		
45	57	3 wks.	11.8	3.48	36.9	106.0	34.0	32.0	1.6	18	+
			2/27/35								
46	68	4 mos.	12.2	4.80	43.6	90.7	25.4	28.0	0.1	5	0
			5/1/35								
			13.2	4.85	44.3	91.3	27.2	30.0			
			7/12/35								
			12.0	4.17	39.1	93.8	28.8	30.7	0.6		
47	60	3½ yrs.	10.8	3.13	32.5	103.8	34.5	33.2	1.7	3	0
48	50	3 wks.	14.5	4.00	42.0	105.0	36.3	34.5	1.2	6	+

TABLE 3.—TOXIC HEPATITIS.

Patient.	Hb.	R B C	Vol., R.B.C.	C. V.	C. H.	C. H. C.	Reticulo-cytes.	Icterus index.	Free HCl.	Duration of symptoms.
	gm. per 100 cc.	millions per c.mm.	cc. per 100 cc.	c. μ .	$\mu\mu$.	per cent.	per cent.			
49	16.2	4.73	49.0	103.5	34.2	33.1	0.3	42	38 (Ewald)	1 wk.
50	16.4	4.32	46.4	107.3	37.9	35.3	0.9	100	44 (Ewald)	2 wks.
	9/5/35									
51	13.9	4.08	44.0	107.8	34.0	31.6	0.8	40		12 days.
	9/20/35									
	13.2	4.33	38.9	89.7	30.5	33.9		Icterus decr.		
52	15.2	4.38	44.3	100.6	31.6	34.3	0.2	60	28 (Ewald)	2 wks.
53	15.0	4.36	43.9	100.7	34.4	34.2	1.5	150	24 (Ewald)	3 wks.
54	13.4	3.82	39.1	102.2	35.0	34.3	0.1	37	40 (Ewald)	1 wk.
55	14.8	4.35	46.3	106.4	34.0	32.0	0.2	66	32 (Ewald)	16 days.

TABLE 4.—OTHER FORMS OF LIVER DISEASE.

Patient.	Age.	Duration of symptoms.	Hb.	R.B.C.	Vol., R.B.C.	C. V.	C. H.	C. H. C.	Reticulo-cytes.	Icterus index.	Anacidity.	Diagnosis.
			gm. per 100 cc.	millions per c.mm.	cc. per 100 cc.	c. μ .	$\mu\mu$.	per cent.	per cent.			
56	39	2 mos.	12.5	3.95	44.6	111.5	31.3	28.3	1.2	180	0	Ca. pancreas (op)
57	54	2 mos.	12.6	3.25	34.3	105.4	38.7	36.7	0.1	107	0	Ca. pancreas.
58	43	3 mos.	12.6	3.37	32.2	95.4	37.3	39.1	1.7	125	0	Ca. pancreas (op)
59	50	3 mos.	11.2	2.76	34.8	126.0	40.6	32.2	1.3	55	0	Diffuse hepatic
												Ca.; cirrhosis(?)
60	56	6 wks.	10.7	3.16	32.7	103.5	33.9	32.7	3.6	90	0	Huge Ca. liver.
61	52	2 mos.	17.0	4.20	48.4	115.2	40.5	35.1	2.2	120	..	Diffuse Ca. liver.
62	19	3 wks.	14.0	4.80	52.0	108.0	29.2	27.0	0.6	187	..	Acute yellow atrophy (P.M.).

may be explained in part, at least, by this degree of reticulocytosis. Of the remaining patients, 4 (Nos. 20, 25, 26, 46) showed a normocytosis and 1 (No. 29) a microcytosis. Patient 32 exhibited a normocytic anemia on admission, but within 4 weeks and concomitant with a rapidly increasing degree of hepatic insufficiency, developed a definite macrocytosis (mean corpuscular volume, 104 c. μ). Although Patient 46 has presented a normocytic anemia to date, a distinct tendency toward the development of a macrocytic type is manifest.

The red blood cell counts were below normal²⁴ in all but one individual (Patient 26). In Patient 46, who showed a persistent macrocytosis, the erythrocyte counts were normal when he first came under observation, but more recent studies have revealed a slight hypocythemia. The lowest count recorded, 1.09 million per cu. mm., was noted in Patient 18, 1 week before exitus, whereas the highest, 4.97 million, was found in Patient 26, who presented the clinical picture of an early cirrhosis. The erythrocytes in this group averaged 3.26 million. In 2 patients, a spontaneous rise in the erythrocytic level was observed synchronously with an improvement in their general condition. Thus, in Patient 11, the red blood cell count rose from 4.05 to 5.26 million in 3½ months, and was accompanied by a more rapid, earlier gain in hemoglobin, from 11.2 to 14.5 gm. per 100 cc. within 1 month. In Patient 15, the erythrocytes rose from 3.75 to 4.23 million in 2 months, whereas the gain in hemoglobin, from 13.8 to 14.6 gm. per 100 cc., may be considered within the normal limits of variation.

The hemoglobin content varied from 5.2 to 16.4 gm. per 100 cc. of blood, with a group average of 12.0 gm. Mean corpuscular hemoglobin values, as observed upon admission, disclosed an hyperchromia in 39 individuals, normochromia in 6 and hypochromia in 3. In subsequent studies, it was noted that Patient 46, with an initial hypochromia, had developed a normochromic anemia. Similarly, the anemia in Patient 19, formerly normochromic, had assumed an hyperchromic character. It is conceded that the accuracy of Sahli hemoglobin estimations is untrustworthy in the presence of moderate or marked bilirubinemia, for the serum discoloration *per se* leads to a high, factitious value. The results are significant, however, since by far the majority of the group showing hyperchromia had either a slight or no bilirubinemia. A spontaneous rise in hemoglobin ranging from 1.4 to 4.1 gm. per 100 cc. occurred in 4 patients (Nos. 9, 11, 12, 19), the largest increment being noted after 7 months of progressive subjective improvement.

Accompanying these remissive tendencies, there has been a decrease in the mean corpuscular volume in 3 patients (Nos. 11, 12, 15), but in none did it return to normal.

Toxic Hepatitis. In all of the 7 patients with acute toxic hepatitis, a macrocytosis was found (Table 3). The increase in the mean cor-

puscular volume was, on the whole, of less magnitude than that in the cirrhoses, the variation being from 100.6 to 107.8 c. μ . It is worthy of mention that in Patient 49 the macrocytosis was already present on the seventh day of illness, and in another (Patient 51), it had disappeared within 2 weeks after improvement set in, indicating the rapidity with which cell changes may take place. A mild anemia was present in 6 out of the 7 patients, and in the remaining one the red blood cell count was normal. The hemoglobin readings were uniformly normal, thus yielding abnormally high mean corpuscular hemoglobin values (hyperchromia). The latter figures, however, cannot be accepted without reservation, for the grade of bilirubinemia in these cases undoubtedly effected an over-estimation of the true hemoglobin content.

Other Forms of Liver Disease. A macrocytic anemia was found in each of the 3 patients with obstructive jaundice due to carcinoma of the head of the pancreas and in the 3 patients with extensive metastatic carcinoma of the liver (Table 4). In 5 of these patients, the mean corpuscular volume ranged between 95.4 and 115.2 c. μ , and the erythrocytes numbered more than 3 million per c.mm. Patient 59, who had a mean corpuscular volume of 126.0 c. μ and an erythrocyte count of 2.76 million, gave a remote history of long standing chronic alcoholism, and, in view of the extreme hardness of the liver, was also suspected of having an hepatic cirrhosis. Perhaps the combination with the latter disease accounts for the greater degree of macrocytosis.

Patient 62, with acute yellow atrophy, exhibited a definite macrocytosis (C. V. = 108 c. μ), with a normal erythrocyte count and a subnormal mean corpuscular hemoglobin concentration.

*Reticulocytosis.** A reticulocytosis varying from 1.1 to 18.0% and averaging 2.47%, was found in 39 out of the 62 patients. This would connote an active erythropoiesis in the majority of our patients. Indeed, Bleichroeder,²⁶ Eppinger,²⁷ Boros²⁸ and Fellingner and Klima⁶ have reported the pathologic finding of red marrow in the long bones, particularly the femur, in some cases of cirrhosis without hemorrhage. No exact correlation between the number of reticulocytes and the severity of the anemia is apparent, although the highest percentages were encountered in 3 of the patients with the more advanced anemia (Nos. 18, 28, 30). It is noteworthy, further, that of 43 patients with icterus, 30 manifested a reticulocytosis.† In contrast, of the 19 individuals without icterus, a reticulocytosis was found in only 9. This has been noted before (Schiff),²⁹ and seems suggestive of a possible relationship between the bilirubinemia and the number of reticulocytes.

* Considerable diversity of opinion exists today concerning the normal percentage of reticulocytes in the peripheral blood.²⁵ For the method employed in this study, the general consensus is that 0-1% is normal.

† Fragility tests were normal.

Relationship of Achlorhydria to the Anemia. Since an achlorhydria in the presence of a macrocytic anemia may denote a deficiency of the "intrinsic factor" of Castle (Isaacs and Goldhamer³⁰), it is of interest to study the incidence of its association with the macrocytic anemia in liver disease. In only 11 out of the 48 patients on whom the gastric acidity could be determined, was a true achlorhydria observed. Wintrobe and Shumaeker⁵ found an achlorhydria in 4 out of 10 patients, whereas Van Duyn¹⁴ observed it in none of his 4 patients. It appears, therefore, that in hepatic disease no correlation exists between the absence of free hydrochloric acid and the development of a macrocytic anemia. Nor is the degree of macrocytosis any greater in those patients with achlorhydria. Wintrobe⁵ has reported the presence of the "intrinsic factor," apparently in adequate amounts, in the gastric juice of a patient manifesting cirrhosis, macrocytic anemia and free hydrochloric acid, which is in accord with our conclusions.

Discussion. The finding of a macrocytosis, almost invariably associated with an anemia, in 89.7% of the patients with cirrhosis and in 91.9% of all the patients with various forms of hepatic disease, is in striking contrast with the incidence as recorded by other observers. Thus, in a study of 57 cases of portal cirrhosis without hemorrhage, King³¹ found none with macrocytosis or with hyperchromic anemia. Wintrobe and Shumaeker⁵ reported a macrocytosis in 11 out of 43 patients (25%) with liver disease. Fellinger and Klima⁶ noted an hyperchromic anemia in 18 out of 48 patients (37.5%) presenting various grades of cirrhosis, but they were of the opinion that practically all such cases, if followed long enough, would ultimately manifest an hyperchromic anemia. They advanced no conclusive evidence to substantiate their belief. In a recent experimental study of carbon tetrachloride cirrhosis in rats, Higgins and Stasney³² observed the progressive development of a macrocytic anemia, in which the macrocytosis and the anemia increased proportionately with the increase in the degree of cirrhosis. Since our patients presented indubitable clinical evidence of widespread liver disease, which in most instances was in an advanced stage, this factor alone would seem to afford an explanation of the higher frequency of macrocytic anemia in our series.

Although the "tendency" to develop a macrocytic anemia in hepatic disease has been noted by Wright,¹³ the transition from a microcytic or normocytic anemia to a macrocytic type, as an accompaniment of increasing liver damage, has been observed by Goodhart,⁹ Van Duyn¹⁴ and by us (Patient 32). The further progressive increase in the degree of macrocytosis and anemia coincident with rapid liver destruction (Patients 18 and 32), together with the presence of the greatest macrocytosis in our patients with the most advanced anemias, or in the terminal stages of cirrhosis, provides clinical corroboration of the work of Higgins and Stasney,³² and

completes a vivid picture of the evolution of the erythrocytic changes. As a corollary to this, it becomes apparent that either a progressive anemia in the absence of hemorrhage, or an increasing macrocytosis, may be utilized as a prognostic guide in chronic or advanced liver disease.

Spontaneous hematologic improvement occurring during the course of hepatic disease, as in Patients 9, 11, 12, 15 and 51, needs engage our interest. Wintrobe and Shumacker⁵ observed improvement in 4 cases of chronic liver disease and during recovery from acute catarrhal jaundice. Similarly, Gram,² Meulengracht,³³ Stewart,¹⁰ and Van Duyn¹⁴ recorded remissions in patients recovering from widespread liver damage with intense jaundice. Hence, it is reasonable to infer, that with the regeneration of liver cells, a restitution of the normal hematopoietic function of the liver may be evoked.

The perplexity of a rising hemoglobin in the face of continued liver destruction, as noted by us (Patient 9) and by others,⁵ remains unsolved. Since our patient presented a bilirubinemia (icterus index, 23), consideration of the clinical evidence favoring the formation of hemoglobin from bile pigment (Patek and Minot³⁴) suggests the possibility of hemoglobin regeneration evolving from the excess circulating bile pigment. Our finding of a reticulocytosis with greater frequency in patients with jaundice seems to offer sustaining evidence in this direction.

The failure in the past to recognize macrocytosis as a frequent concomitant of widespread liver disease may be satisfactorily explained. The inadequacy of cell diameter measurements and of Price-Jones frequency curves on the blood of patients with an erythrocyte count in excess of 3 million per c.mm. has already been emphasized by Haden³⁵ and by Wintrobe,²¹ for results may be obtained which deviate so little from normal, that they possess very limited if any diagnostic value. That the average erythrocyte count for our series was 3.42 million per c.mm. bears recapitulation at this point. Further, measurements of the cell diameter do not take into account the three dimensional variations in size, a fact best illustrated by Haden's³⁶ cogent observation: "An average increase of 1 micron in the diameter of an erythrocyte increases the volume 44% if the thickness is increased in the same ratio." From the blood smears of our cases, the cells appeared to be slightly enlarged but quite uniform in size when the red cell count was greater than 3.5 million per c.mm., only an occasional outstanding macrocyte being seen in some cases. In the more advanced anemias, a conspicuous macrocytosis, slight or moderate anisocytosis, a relatively slight poikilocytosis and, in some, an occasional microcyte were in evidence. Routine examination of a blood smear may, therefore, fail to reveal any macrocytosis in the average case. By the use of an hematocrit, it is likely that a macrocytosis will be

found in liver disease, more particularly in the advanced forms, with much greater frequency than heretofore.

Several hypotheses have been propounded in explanation of the origin of the macrocytosis and anemia. Naegeli³⁷ and Holler and Kudelka¹⁷ thought the anemia was due to an endogenous toxic effect upon the red blood cells. Meulengracht³³ believed the macrocytosis to be dependent upon alterations in the blood plasma, resulting in a swelling of the cells. His observation that the diameter of the erythrocytes varied directly with the intensity of the icterus, as well as the lack of evidence in his cases pointing to a new formation of red blood cells, favored his belief. He felt that possibly the bile acids were responsible for this change. Capps, at an earlier period, had entertained this hypothesis, but rejected it on the grounds that simple swelling of red cells could not account for the high color index. He concluded that a macrocyte rich in hemoglobin must result from abnormal cell development, not from simple osmosis. It is apparent from our studies that the occurrence of macrocytosis in the absence of icterus, and its persistence in some cases long after the icterus disappeared, together with the evidence of erythropoiesis (reticulocytosis) in many patients, are at variance with the above observations of Meulengracht, and tend further to refute his hypothesis as the sole explanation.

Perrin³⁸ regarded the anemia as secondary to hepatic insufficiency, and administered liver to his patients with apparent subjective and hematologic improvement. More recently, Boros¹¹ concurred in this view, and believed that the secondary, increased erythropoiesis introduced many macrocytes into the blood.

Castle and his coworkers³⁹ have pointed out that the common factor in the production of macrocytic anemia is the failure of a specific reaction between the "extrinsic factor," present in food, and the "intrinsic" gastric factor; in many, the combination of a gastric defect and partial dietary deficiency appears to produce the same effect as the total absence of either factor. Failure to absorb or utilize the hematopoietic product of this interaction* may produce a similar effect. That this active substance is stored in the liver was first demonstrated by Ivy, Richter and Kim.⁴⁰ Hence, an extensively damaged liver, being incapable of storing sufficient amounts of the hematopoietic principle, might be accompanied by a macrocytic anemia.^{15,19,23} Goldhamer, Isaacs and Sturgis¹⁹ have corroborated the work of Ivy *et al.*, and have found the active substance either reduced or absent in hepatic cirrhosis with macrocytic anemia. In a case of acute yellow atrophy with macrocytic anemia, they found that the active principle, although present in the liver, apparently was not utilized by the body. Whipple and Robschey-

* The work of E. A. Greenspon (J. Am. Med. Assn., 106, 266, 1936) seems to indicate that the hematopoietic principle is normally elaborated and secreted by the gastric mucosa, an "extrinsic" factor being unnecessary.

Robbins,⁴¹ studying the hemoglobin production factors in the human liver, observed the lowest values in cases of severe liver injury with anemia. Thus, the view of a deficient storage or utilization of the active hematopoietic principle by a defective liver seems at present to be the most tenable explanation of the macrocytic anemias in liver disease.

In evaluating the cause of the anemias in our cases, cognizance must be taken of the possible rôle of chronic alcoholism, a history of which was elicited in 65% of the patients with cirrhosis. The resultant dietary deficiency noted in 6 patients with macrocytic anemia, as manifested by polyneuritis,⁴² or glossitis,⁴³ or both, is of singular importance, and probably contributed in no small measure to the development of the anemias. Eliminating these 6 cases, the incidence of macrocytosis is approximately the same (91%). In view of the frequency of chronic gastritis attendant upon chronic alcoholism, perhaps in some of the cirrhoses the combination of a gastric defect and mild dietary deficiency might have been provocative of a macrocytic anemia. This is not ascertainable from the data at hand, but if these cases too are excluded from consideration, the incidence of macrocytosis among the remaining 30 patients with widespread or advanced liver disease is approximately 87%. Excepting the cases of manifest dietary deficiency, it would appear that, for the most part, factors other than hepatic insufficiency played a relatively insignificant rôle in our series.

The possibility of the macrocytosis having been due in some cases to acidosis deserves consideration. Although the carbon dioxide combining power of the bloods was not determined, clinical evidence of acidosis was absent and urine examinations were normal.

It may be of interest to direct attention to the subnormal mean corpuscular hemoglobin concentrations* found in 20 cases with macrocytosis. In 1 of these, the value has gradually risen to normal; in 3, although it has increased, the value is still subnormal. In 6 of this group, hyperchromia was not present. From these results, one might speculate that the chronologic sequence of the cell changes consists of a more or less transitory swelling of red blood cells, followed by an elevation in the hemoglobin to a normal or hyperchromic level and, as a result of an insufficient amount of hematopoietic substance, by the subsequent appearance of true macrocytes. The initial increase in cell volume might result from a lowered colloid osmotic pressure secondary to the decrease in the serum albumin fraction,⁴⁴ so frequently found in hepatic insufficiency, or in advanced hepatic disease.⁴⁵ Such an hypothesis gives prominence to Meulengracht's original idea, but only in a restricted sense. Further studies, however, are essential for a better understanding of these blood changes.

* Values greater than 32% were considered normal.

The treatment of this anemia by parenteral liver extract has, in most cases, been disappointing.^{5, 6, 9, 46} Only in several instances have satisfactory results been attained.^{5, 9, 19, 22} Of 5 patients treated intensively with a potent extract, none showed hematologic improvement, although in 2 a slight reticulocyte rise occurred. It seems likely that the liver is essential for the intermediary metabolism of liver extract, converting it into an effective hematopoietic substance. In this way, we may account for the varied results following liver therapy in patients with hepatic disease, little or no response being elicited in cases with extensive liver damage.

Summary. 1. The morphologic changes in the blood of 62 patients with various forms of widespread or advanced hepatic disease are recorded.

2. Either a macrocytic anemia or macrocytosis alone was found in 91% of the patients.

3. Spontaneous hematologic improvement may occur in the course of acute or chronic hepatic disease.

4. Clinical evidence pointing to a relationship between the degree of macrocytosis and anemia and the extent of hepatic insufficiency is presented, and its prognostic significance is indicated.

5. A reticulocytosis occurred in 39 patients and was more common with bilirubinemia. The implications are discussed.

6. Achlorhydria is not essential for the development of macrocytic anemia in liver disease.

7. Macrocytosis in liver disease may possibly result from a primary swelling of the erythrocytes, followed by the secondary appearance of true macrocytes.

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ANEURYSM OF THE ABDOMINAL AORTA: A STUDY OF 73 CASES.

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FOLLOWING experience with several cases of aneurysm of the abdominal aorta, it was thought desirable to study all such cases admitted to the wards of Charity Hospital in the past 30 years. All authors discussing the condition point out the infrequency of such aneurysms. Because of the high rate of syphilis among the negroes admitted to this hospital, it offers an ideal place to collect a group of cases.*

* Since this paper was written, there have been 4 additional cases: 1, a colored female, aged 38, presenting erosion of vertebrae upon roentgen ray study; 2 males, 1 white, aged 53, and 1 colored, aged 38, died from rupture of the sac, proved at necropsy. Another, a colored male, aged 51, was studied on the author's ward; he presented pulsation in the left paravertebral region, a palpable mass, and by the roentgen ray erosion of the last two dorsal, and first lumbar vertebrae as well as the twelfth rib. These 4 cases, with the 1 mentioned in the section on diagnosis and not included in the statistics, brings the total number of cases to 73.

This paper is based on a study of 68 cases of abdominal aneurysm. All but 3 arose from the abdominal aorta. Three arising from the celiac axis were included, for they could not be differentiated from the others except at necropsy. Cases were chosen for consideration only when good evidence was available to make the diagnosis a certainty. Thus the diagnosis was proven at necropsy in over one-half the cases. In the others the roentgenologic and physical features were considered sufficient. Exploratory laparotomy made the diagnosis in 2 cases. A number, equal to almost one-half the accepted cases; were discarded because of lack of data substantiating the diagnosis of aneurysm of the abdominal aorta.

Incidence. Aneurysm of the abdominal aorta is encountered infrequently in anyone's clinical experience. No extensive collection of cases has been made since Nixon's appeared in 1911.

Bryant,¹ in 1903, reported the necropsy cases showing this lesion at Guy's Hospital from 1854 to 1900. During this period in 18,678 autopsies there were 325 aneurysms of the aorta, of which 54 (16%) were of the abdominal aorta.

In 1905, Osler² reported 16 cases which had been found in 16 years among 18,000 ward admissions at Johns Hopkins Hospital, an incidence of 1 abdominal aneurysm to 10 thoracic aneurysms. In the first 200 necropsies at that institution there had been 49 aneurysms of the thoracic aorta and 11 of the abdominal aorta. This author called attention to variation in incidence in various localities, pointing out that in a series from Vienna there had been 3 abdominal aneurysms in 222 aortic aneurysms found in 19,300 autopsies.

In a monograph not available to me, Nunneley reported 32 cases of abdominal aortic aneurysms which occurred among 17,872 autopsies done at St. George's Hospital over a period of 65 years. These are included in Nixon's series which follows:

Nixon,³ in reporting a case of aneurysm of the abdominal aorta due to congenital syphilis in a girl, aged 20, collected 233 cases.

In 1918, Marlow and Doubler⁴ reported a case of abdominal aortic aneurysm with rupture into the duodenum. At this time they collected 11 more cases of abdominal aneurysm reported since Nixon's paper, bringing the total to 244 cases. Of this whole group, they had been able to find only 5 cases with rupture into the gastrointestinal tract.

From this last paper to the present date I have been able to find reports of 69 more cases, all of which have appeared as single case reports, except for a few. Gernert⁵ published 6 instances of abdominal aneurysm found among 28 aortic aneurysms in 1062 autopsies. Dafoe⁶ reported 2 cases of ruptured abdominal aneurysms due to tuberculosis, the diagnosis being established microscopically. Farmer,⁷ in describing bone absorption in the spine due to abdominal aneurysm, reported 3 cases.

Thus, up to the time of the writing of the present paper, there have been reported, in the literature, about 313 cases of abdominal aneurysm. This paper adds 68, bringing the total to 381 cases. Among these have been 9 cases with rupture into the gastrointestinal tract to which this paper adds another, a case with rupture into the stomach.

The 68 acceptable cases considered in this paper were found at Charity Hospital over a 30-year period, in which time there were 215,516 medical admissions. Of this series, 38 were proven at autopsy, in a total of 12,053 necropsies during this time. During the 30-year period the diagnosis of aortic aneurysm was made 976 times. In a recent study the author made of these, 532 were accepted as cases of unquestionable aneurysm. Considering then, undoubted cases, the incidence of abdominal aneurysm is 1 to 7.8 cases of thoracic aneurysm.

Etiologic Factors. *Race.* As was to be expected, the greatest number of aneurysms occurred among the negroes. Not that that race in itself is a major factor—though I am inclined to believe in a greater tendency to vascular disease in the colored person—but because of the higher incidence of syphilis. Fifty-four (79.4%) were negroes, whereas 14 (20.5%) were whites.

Sex. Because of the specific etiology of aneurysm, and possible effect of physical labor, the frequency of aneurysm of the abdominal aorta would be expected to be greater among the males. Thus 57 (83.7%) of the patients were males. Nixon, in his 233 collected cases, found 207 (88.8%) to be in males and 26 (11.2%) in females.

Occupation. This was recorded in 50 cases; 44 of these did physical work. Most were common laborers, but others whose work was manual were farmers, sailors, mechanics and carpenters. Among the women were 5 whose occupation was heavy housework and 1 that of a dressmaker.

TABLE 1.—DISTRIBUTION AS TO AGE, SEX AND COLOR.

Age in years.	Colored males.	White males.	Colored females.	White females.
20 to 24	3	..	3	
25 to 34	8	5	3	
35 to 44	20	2	2	
45 to 54	9	3	..	1
55 to 64	4	1	..	2
65 and up	1			
No age given	1			
Total	46	11	8	3

Age. Aneurysm is usually considered to be a disease of the fourth and fifth decades. In this group, 6 patients, all colored, were found to be between 20 and 25 years; 22 (32.3%) were under 35 at the time of admission to the hospital; 46 (67.6%) were under 45. Table 1 indicates the distribution of cases as to age, sex and race.

Syphilis. The *Treponema pallida* is undoubtedly the most frequent specific agent in the production of aneurysm. The Wassermann reaction is naturally not necessarily positive in syphilis. The test was carried out in 39 cases and not recorded in 29 cases. Of the 39 recorded reactions, 19 (48.7%) were positive and the balance negative. A history of penile sore was obtained in 28 cases. Of these, 8 presented a positive Wassermann reaction, 12 a negative and in 8 no record of a blood Wassermann was available. (Antisyphilitic treatment had been administered in 11 cases, of which 6 showed a negative Wassermann test.) If we add the 20 cases in which the history of a penile sore was obtained, but in whom the Wassermann reaction was either negative or not recorded, to the 19 cases in whom a positive reaction was obtained, we have as evidence of syphilis either a history of chancre or a positive Wassermann reaction in 39 cases (57.3%). Unfortunately it is only in recent years that the necropsy protocols describe microscopic examination of lesions. Therefore, microscopic evidence of syphilis appears in only 5 cases of the 38 that came to necropsy. In an additional 9 cases the gross lesions of the aorta were described as being syphilitic.

Arteriosclerosis. It is accepted that with marked atheromatous changes of the aorta, as are seen in older age groups, aneurysm of the aorta may occur. Kampmeier and White⁸ reported such a case in which the most extreme atheroma of the aorta was present. They reported this case because of the association of a dissecting aneurysm of the descending arch with an aneurysm of the abdominal aorta. It is possible that in a very few of this group, aneurysm may have originated on the basis of atheroma. Only 8 were above 55 years and only 1 above 65.

Tuberculosis. This etiologic factor has been described by Dafoe.⁶ He reported the only 2 such cases in which tubercles were demonstrable microscopically. In the literature this author was able to find only 11 cases of aortic aneurysm due to tuberculosis, all of them being of the thoracic segments. Tuberculosis may cause aneurysm by involvement of the intima, by lesions of the media or adventitia, though infection *via* vasa vasorum, or lastly by extension from tuberculous lymph nodes, abscess or bone lesion. (We have seen 1 case of aneurysm of the aortic arch due to extension from tuberculous lymph nodes.)

Trauma. Crushing injury to the abdomen, with probably interruption of the integrity of the aortic wall, has been rarely described as a cause of aneurysm of the abdominal aorta. Apparently none of the cases in this series presented the etiologic factors which would place them into either of these last two classes.

Symptomatology. Eight cases were admitted to the hospital either practically moribund, or died so soon after that no history was obtained.

Pain was the most frequent symptom, being present in 55 (91.6%) of the 60 cases giving a history. It made up the admitting complaint in almost this number. The pain was remarkable in its wide distribution. However, in most cases the pain was referred to one of several sites. Most frequently the pain was localized to the abdomen, namely, in 32 patients. Of these, 10 specifically named the epigastrium as the site, 1, the left lower quadrant, and 3, the left side of the abdomen.

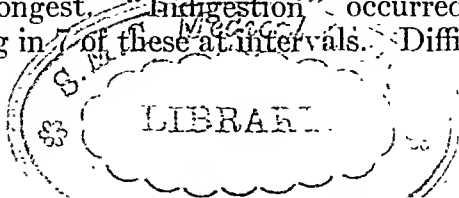
The next most frequent site of pain was the back. In 20, pain was present in this region distributed as follows: 11 patients localized the pain to the middle of the back, 6 to the left lumbar region, 2 to the right sacroiliac area, and 1 to the lower back. One patient referred pain to the left hip and thigh, 1 to the left thigh and knee, and a third to the right thigh. In 1 patient pain was localized to the right chest, and in another to the precordial region. In some patients pain was referred to more than one site.

Radiation of the pain from the original sites as described above was generally downward. In 6 patients the pain was referred to the left lower extremity, to the thigh alone, or to the thigh and leg, and in one to the foot. In the thigh the inner and outer aspects were described as being affected. Radiation was to the right thigh in 3 cases. The left groin was the site of radiation in 2 and to both legs in 1. Unusual was pain radiating to the left shoulder in 2 cases. There was roentgenologic evidence of erosion of lumbar vertebræ in 10 of the cases in which radiation of pain was downward. Radiated pain was no doubt due to root involvement.

Pain was described as being constant in 21 of the 55 cases presenting pain. It was intermittent in character in 12. In the rest, no description was available. Several patients complained only of pain after meals. Among the group complaining of constant pain were some who described the pain as having been intermittent at first, but with the progress of the disease it had acquired the characteristic of being practically constant. Quite frequently statements were made that pain was especially worse at night, or that it was particularly aggravated when lying down.

The type of pain varied greatly, though the severity was stressed by most patients. Pain was often described as being throbbing, synchronous with the heart beat, in others it was like a knife thrust, or lancinating, in many it was said to be of an aching character. A few patients described the pain as being colicky in nature, and in others as stinging sensation; 22 stated the pain had been getting progressively worse, and only 1 admitted improvement in pain.

The presence of tumor, as recognized by the patient, was recorded 9 times; in 8 it was abdominal and in 1 the left flank. A mass had been noted for varying lengths of time, from 1 month, the shortest, to 2½ years, the longest. "Indigestion" occurred in 12 cases, nausea and vomiting in 7 of these at intervals. Difficulty in urina-



tion and dizziness were noted in 1 each. Loss of weight was complained of in 23 patients, the amount, varying from a few pounds to as much as 35 pounds. In Table 2 are listed the symptoms which were found in this group of aneurysm cases.

TABLE 2.—SYMPTOMS IN 60 CASES.

Symptom.	No. cases.	Symptom.	No. cases.
Pain:		Pain:	
Abdomen, general	18	Lower extremities	3
Epigastric	10	Right chest	1
Left abdomen	3	Precordium	1
Left lower quadrant	1	Tumor mass	9
Middle back	11	"Indigestion"	12
Left lumbar	6	Vomiting	7
Right sacroiliac	2	Dysuria	1
Lower back	1	Loss of weight	23

Two patients gave no data in their histories which suggested abdominal disease, their story being that characteristic of cardiac failure. In a third patient the history was typically that of a carcinoma of the esophagus which was the cause of death as proven at necropsy, the abdominal aneurysm being coincidental.

The duration of symptoms is of interest. Cases of more than 1 year's duration were very few. In 57 cases, where the history of duration of symptoms was given, it was found that in 35 (61.3%) the symptoms were of 6 months' or less duration, and that in 51 (87.7%) the symptoms had been present no more than 1 year. Duration can best be considered in table form (Table 3):

TABLE 3.—DURATION OF SYMPTOMS IN 57 CASES.

Duration.	No. cases.	Duration.	No. cases.
1 wk. or less	5	9 to 12 mos.	12
1 to 4 wks.	2	12 to 18 "	2
1 to 3 mos.	12	18 to 24 "	1
3 to 6 "	16	2 to 3 yrs.	2
6 to 9 "	4	8 yrs. (questionable)	1

Physical Findings. Except for the abdomen, the physical examination in most of the patients did not reveal any remarkable findings. The few extraneous signs which were noted will be briefly enumerated after the abdominal findings have been described.

On inspection, fullness of the abdomen was noted usually of either the epigastric or of the left subcostal regions. These findings were recorded in 10 cases. Visible pulsation was noted in a few of these. In 3 cases the aneurysmal sac pointed posteriorly with visible tumor in the back. One of these presented a tumor the size of a grapefruit projecting to the left of the spine, having eroded the lowest 3 ribs on that side. The second similar case had a tumor described as the size of a fetal head, projecting 6 cm. above the level of the surface and located to the left of the spine from the tenth dorsal to the third lumbar vertebra. The third presented a mass the size of one-half coconut to the left of the spine and below

the ribs. Dilated veins over the abdomen were described in 4 cases and dilated veins over the right thigh in 1.

A tumor in the abdomen was described upon palpation in 47 (60.3%) of the cases. In 3, described above, where the sac pointed posteriorly, no mass was described in the abdomen, though examination may not have been as careful in the face of the obvious lesion. In the remaining 18 cases no tumor was described, though in 2 the abdomen was too rigid for satisfactory examination. Pulsation was described in 2 others, but no mass was noted. Site of the mass was most frequently found to be epigastric or in the left subcostal region. The tumor was epigastric in location in 24 (50%) of the 47 cases presenting abdominal tumor. In 10, it was at the left subcostal margin. The sac was found lower in the abdomen at the region of the umbilicus, though usually to the left of it in 8 cases, in 1 of which the tumor extended from the subcostal margin to the crest of the ilium. A mass in the left renal region was noted in 3 cases. In 2, the tumor was located in the right abdomen, 1 in the lower quadrant and 1 to the right of midline in the upper abdomen.

The description of the size of the tumor varied a great deal, terms of common objects being usually used to describe the size. The tumors were described as the size of a grapefruit, baseball and closed fist; 9 were said to be the size of an orange and 9 were merely described as being large; 4 varied from 7 to 15 cm. in diameter. In the balance of the cases no description of size was given.

In the 50 cases in which tumor was described, pulsation of the tumor mass was recorded in 49. Aside from the cases with the sac projecting posteriorly, 4 other cases in which the mass was felt anteriorly showed definite palpable or visible pulsation in the left lumbar region. Thirty-nine (79.6%) demonstrated an expansile type. A palpable thrill was present in 3 cases. A bruit, systolic in time, was heard over the sac in 26 (52%) of the cases of pulsating tumor. Tenderness on palpation of the mass was present in a high percentage of the cases, and in 6 tenderness was also noted in the left flank or left lumbar region. Rigidity of the abdomen on palpation was often found, especially on the left side.

The rest of the physical findings were more or less incidental. Lag and limited excursion of the left lung base occurred in a few cases. Impairment of the percussion note at the left base, distant or changed breath sounds, and râles were noted in an occasional case. A friction rub was heard at the left base in 2 cases. Cardiac enlargement was recorded in 14 cases. The murmur of aortic regurgitation was recognized twice. One patient presented neurologic disturbances of the left lower extremity due to pressure on the spinal roots.

Roentgenologic Findings. The roentgenologic examination has in more recent years been found to be of exceeding importance as an

aid in the diagnosis of suspected aneurysm of the abdominal aorta. This is clearly shown in the more recent half of this series of cases. The data which will be shown to be important criteria in diagnosis has been gathered from cases seen in the last 10 to 15 years at Charity Hospital.

The Roentgen ray was used in 32 (47%) of all cases for assistance in the specific diagnosis of abdominal aneurysm. In 3 cases it was used with other diagnoses in mind, namely, studies for renal calculus and gastro-intestinal disease, which were negative, and in 1 case of carcinoma of the esophagus.

The most important roentgenologic finding is that of pressure erosion of vertebrae. Studies of the spine were made in 24 of the 32 cases. In 18 of these (75%) erosion of the vertebrae was made manifest; 4 of this group also showed gastric displacement by the sac as well as erosion. In 6, studies of the spine were negative. Of the 8 cases in which the Roentgen ray was used in studies exclusive of those of the spine there were 5 in which fluoroscopic examination was used, showing in 4 a pulsating tumor, the fifth being negative. In 1 of the 4 was recorded gastric deformity by a pulsating mass. Of the remaining 3 cases in which the Roentgen ray was used as an aid, with abdominal aneurysm in mind, was 1 in which the shadow of the sac was obtained by use of pneumoperitoneum and 2 in which flat plates were used, 1 being positive and 1 negative. As a result we see that in 32 cases in which the Roentgen ray was used with the tentative diagnosis of abdominal aortic aneurysm, it gave a positive answer in 24 (75%) of cases. Calcium deposit in the wall of the sac was seen in 3 cases.

TABLE 4.—VERTEBRÆ ERODED IN 18 CASES.

	No. cases.		No. cases.
Dorsal, eleventh	2	Lumbar, second	8
Dorsal, twelfth	9	Lumbar, third	1
Lumbar, first	16		

Erosion of the vertebrae, being of such importance, should be described in a little more detail. In 2 cases there was erosion of 1 to 3 of the lower ribs as well as of the vertebrae. Of the 18 cases showing erosion, all but 3 presented involvement of 2 or more vertebrae. The most frequent combination was erosion of the twelfth dorsal and first lumbar vertebrae (Table 4). The erosion seen is characteristically of the anterior and left lateral aspects of the vertebral bodies. The intervertebral disks are not involved in this destruction (Fig. 1).

Diagnosis. From the records it was impossible to learn how frequently the correct diagnosis of abdominal aneurysm was made. But from the request blanks addressed to the Roentgen ray Department in recent years, it is evident that such a tentative diagnosis was made in a fairly high proportion of the cases. In



FIG. 1.—The arrow indicates erosion of the body of a vertebra as shown by the Roentgen ray.



FIG. 2.—Pressure erosion by aneurysm of the abdominal aorta, characteristically involving vertebral bodies, leaving intervertebral disks intact.



such, an abdominal tumor presenting expansile pulsation led to a diagnosis.

As every clinician knows, an abdominal tumor accompanied by pulsation is not uncommon. Ordinarily, the pulsation is merely transmitted from the aorta lying posterior or adjacent to the tumor, whatever its origin. However, if the examination permits the grasping of the tumor between the two hands, one on either side, and thus presents expansile pulsation, the diagnosis of abdominal aneurysm may justifiably be entertained. As was noted above, expansile pulsation was demonstrated in about 80% of 49 cases presenting tumor with pulsation. Confirmatory evidence is a systolic bruit heard over the tumor, and a palpable thrill. In the presence of a tumor with expansile pulsation, or any other tumor suspected for one or another reason of being an abdominal aneurysm, the Roentgen ray frequently offers evidence of greatest importance in arriving at or in confirming the diagnosis. Erosion of the lumbar vertebræ, especially without destruction of the intervertebral disks is practically pathognomonic of aneurysm. As was discussed above, these findings appeared in over one-half of the cases in which the Roentgen ray was used for its assistance in the diagnosis of this lesion. Since the abdominal aneurysm usually is due to syphilis, the Wassermann reaction may be of assistance, but we cannot place too much reliance on this feature in diagnosis. Early in the paper I discussed evidence of syphilis in this series. Further, due to the high incidence of syphilis among the negroes admitted to Charity Hospital, we must constantly consider other diseases coincident with syphilis.

The diagnosis of an abdominal aneurysm may not be considered and the diagnosis is impossible in some cases, as was demonstrated in a recent case, not included in this series, seen at a clinicopathologic conference. A male, aged 38, had for over a year complained of lower lumbar stiffness and slight pain. He was admitted to Charity Hospital a second time for this complaint. A diagnosis of lumbosacral arthritis was made and apparently confirmed by the Roentgen ray. Sudden death occurred. At necropsy was found an aneurysm about the size of a large orange just beneath the diaphragm where it could not have been palpated. It had ruptured into the left pleural cavity and had infiltrated the left leaf of the diaphragm and the retroperitoneal region of the left side. The vertebræ were deeply eroded (Fig. 2). If the Roentgen ray plate had included the upper lumbar vertebræ the diagnosis would have been made.

Several conditions must be considered in the differential diagnosis. Accentuation of normal pulsation of the abdominal aorta, as may be seen in advanced arteriosclerosis, or in the thin neurotic patient may suggest aneurysm. However, careful examination shows the absence of tumor and expansile pulsation.

Spinal arthritis may be simulated as indicated above, possibly due to involvement of the spinal roots. This diagnosis was made in several of the patients in this series. The presence of a pulsating tumor should point toward a diagnosis, and the Roentgen ray would give evidence for or against aneurysm with vertebral erosion or spinal arthritis.

Tumor of the liver, including malignancy, primary or metastatic, gumma, or abscess of the left lobe, of which we have recently seen 2, may at first glance simulate an aneurysm because of transmitted pulsation. However, the absence of expansile pulsation, the mobility of the tumor with respiration, and the usually palpable liver edge make the diagnosis without question.

Gastric carcinoma may present tumor with transmitted pulsation and may raise the question of abdominal aneurysm. If the tumor is movable with respiration, aneurysm is ruled out. A fixed carcinoma, due to extragastric extension, is diagnosed by lack of expansile pulsation, and by laboratory and roentgenologic studies of the stomach. It must be recalled that an aneurysm may cause a filling defect of the stomach due to extrinsic pressure.

In the past couple of years, we have seen pancreatic cysts simulate abdominal aneurysm. Both conditions present a tumor, and the cyst may present a transmitted pulsation which displaces the cyst laterally with each systole, simulating in a way an expansile pulsation. Further, in Roentgen ray studies made in the lateral position both may show displacement of the stomach anteriorly. We have seen both lesions with calcified walls. The diagnosis must rest on careful study of the pulsation; if erosion of vertebræ is present the diagnosis of aneurysm is made.

Differentiation of aneurysm from a mass of malignant retroperitoneal lymph glands may be still more difficult. Transmitted pulsation may be present, anterior displacement of the stomach with pressure defect may occur and erosion by invasion of the vertebræ may take place. In malignancy, however, the intervertebral disks are not spared, as they are in erosion due to aneurysm.

Renal tumor was considered in several cases of this series, and pyelography was resorted to in 1 case. Diagnosis is made on the basis of type of pulsation and the use of the Roentgen ray for spine and kidney studies.

Lastly, it must be recognized that, due to a thick laminated clot in the sac, no pulsation may be present, or at least be of such slight degree that expansibility cannot be determined. In such event the differentiation of aneurysm from some of the above conditions may be very difficult, if not impossible.

Prognosis and Death. Abdominal aneurysm is apparently a condition in which death may be expected within a short time after the onset of symptoms. In the series of 68 cases, death occurred in the hospital in 46 instances (66%). Death occurred within

1 month of hospitalization in 38 and in over one-half of these took place in less than 1 week after entering the hospital. Table 5 gives the time elapsed from admission to the hospital to death in the 46 cases. By a correlation of this table with Table 3 it can be readily seen that the majority of patients with abdominal aneurysm succumb to the process within 6 months from the time of onset of symptoms.

In 20 of the 46 patients dying in the hospital, death was described as being sudden, instantaneous or occurring in a few minutes. Death took place rather quickly, apparently a matter of several hours in 10 cases. Bleeding took place for 12 to 72 hours in 6 cases, as one might judge from notes as to coma, apparent loss of blood, with later necropsy. No note was made as to the rapidity of fatal issue in 9 cases. One patient obviously died of carcinoma of the esophagus, abdominal aneurysm being an incidental finding.

TABLE 5.—TIME FROM ADMISSION TO DEATH IN 46 CASES.

	No. cases.		No. cases.
1 to 3 days	17	4 to 8 wks.	2
3 to 7 "	10	2 to 3 mos.	4
1 to 2 wks.	3	5 to 6 "	1
2 to 4 "	9		

Death is due to rupture of the abdominal aneurysm in the majority of cases. As will be seen in the discussion of pathologic findings, this is most often retroperitoneal. The rapidity with which death ensues is related to the degree of rupture. Most often there is sudden exsanguination. However, we not infrequently see, in aneurysms of the thoracic aorta, that slow leakage of blood may occur with slower progress to death. Such circumstances were apparently at work in several cases of this series where death was not sudden, but still due to hemorrhage. Of the 38 cases coming to necropsy, 31 showed death due to hemorrhage. Nixon reported 152 deaths from rupture in his collected series of 233 cases. Among the 7 deaths from other causes, there were no sudden deaths, though 2 died in a few hours. Death by hematemesis occurred in 2 cases, 1 of which came to necropsy and showed rupture of the aneurysm into the stomach.

Pathologic Findings. Necropsy was performed in 38 cases. The sac in all of these arose from the abdominal aorta except in 3 in which the sac originated from the celiac axis. These were included in this study, however, for it would be impossible clinically to differentiate such aneurysms from those arising from the aorta itself.

In practically all cases the sac arose from the upper part of the abdominal aorta, that is, from the portion between the level of the renal artery and the diaphragm. The size of the sac varied from that of a hen's egg to that of the head of a child; commonly, the size was given as that of an orange or grapefruit. Practically all sacs contained laminated clots.

As noted above, death was due to rupture of the sac with hemorrhage in 31 of the 38 cases coming to necropsy. The hemorrhage was retroperitoneal in 15, about equally divided as to frequency on the right and the left side of the spine. Rupture was retroperitoneal in 1 case with subsequent rupture into the peritoneal cavity. In 4 cases, rupture was directly into the peritoneal cavity. Bleeding between the leaves of the diaphragm occurred in 2 cases. In 4 cases, in which necropsy was done by the coroner, it was merely stated that rupture had occurred, the site of bleeding not being given. It is of interest that in 3 cases rupture took place through the left leaf of the diaphragm into the left pleural cavity. In another case, the sac being adherent to the diaphragm, the blood infiltrated the diaphragm, posterior mediastinum, penetrated about the roots of both lungs and finally perforated into both pleural cavities. One of the aneurysms of the celiac axis ruptured into the stomach, with death by hematemesis.

Erosion of vertebræ was described in 13 of the necropsy protocols. Left-sided pleural effusion occurred in 4 cases. Other incidental pathologic findings were pulmonary tuberculosis in 1, aneurysm of the ascending arch in 1, carcinoma of the esophagus in 1 and cardiac hypertrophy in 4 cases. The anatomic evidences of syphilis were described under the section on Etiology.

Summary. Aneurysm of the abdominal aorta is a relatively uncommon lesion. From the records of Charity Hospital for the past 30 years there have been selected 68 such cases in which the diagnosis could not be questioned. This group is the largest which has ever been collected from any one institution.

The etiologic factors in the production of aneurysm of the abdominal aorta have been discussed, and the clinical features have been described.

Roentgenologic findings, of great importance in diagnosis, have been emphasized. Diagnosis of abdominal aortic aneurysm involves the consideration of a number of conditions and may be difficult or even impossible.

Prognosis in this lesion is poor, the majority of patients dying within 6 months from the onset of symptoms. Death is usually sudden and due to rupture of the aneurysm. The necropsy findings in 38 cases have been presented.

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ABDOMINAL PAIN OF VASCULAR ORIGIN.

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VASCULAR disease is not generally recognized as one of the causes of abdominal pain. Although so-called abdominal angina has been described for years, a lack of postmortem evidence has prevented its acceptance as a clinical fact. Thus, Sir William Osler and Sir Clifford Allbutt both favored the view that transient attacks of abdominal pain in arteriosclerotic individuals were manifestations of angina pectoris rather than of visceral arterial disease, and more recently Morley¹ has written that there is no evidence of vascular pain in the abdomen apart from that due to actual gangrene and peritonitis secondary to mesenteric vascular occlusion. Conner² has renewed interest in this subject by concluding on theoretical grounds that visceral arterial disease is analogous to coronary disease and plays a significant rôle in many hitherto undiagnosed cases of abdominal pain.

If, as Conner suggests, visceral arterial disease is analogous to coronary disease, the past histories of patients dying of mesenteric thrombosis ought to reveal evidence, in a certain percentage of cases, of chronic abdominal pain preceding the acute attack. With this point in mind, the histories of all patients dying of mesenteric vascular occlusion, confirmed by autopsy, in the Peter Bent Brigham Hospital have been reviewed. In 7 of 12 cases in which the occlusion was associated with arteriosclerosis, there was a story of chronic recurrent abdominal pain preceding the fatal attack by weeks, months or years. In all of these cases mesenteric arteriosclerosis appeared to be the most plausible cause of the abdominal pain but unfortunately in nearly every case varying degrees of coronary sclerosis rendered a convincing interpretation of the cause of the pain impossible. The following case, however, was selected as indisputable evidence of the occurrence of abdominal pain of vascular origin.

Case Report. E. W., a male laborer, aged 47, entered this hospital because of recurrent abdominal pain of 2 months' duration. At the onset of the present illness the pain was located about the umbilicus, did not radiate, and was definitely related to meals, occurring about 1½ hours after eating. The patient described it as a "hard lump in the stomach." He

thought that for a short time the taking of a daily enema and mild cathartics, and the avoidance of heavy meals had alleviated the pain, but the severity of the attacks gradually increased. On several occasions there was slight diarrhea but no nausea or vomiting. Studies at another clinic, including an Roentgen ray examination of the entire gastro-intestinal tract, were negative and the patient was discharged with a diagnosis of psychoneurosis. Four days later he was admitted to this hospital.

At the time of admission the pain was excruciating and constant. It was now associated with nausea and vomiting, but there was no jaundice, diarrhea or melena. On physical examination the patient was found to be well developed, but had obviously lost weight recently. Examination of the heart and lungs was not remarkable. There was very slight tenderness to deep palpation in the epigastrium, but there was no muscle spasm or distention. The leukocyte count was 20,000 per cmm. The erythrocyte count was 5,000,000 per cmm. The blood Wassermann test was negative, and the examination of the urine and cerebrospinal fluid was negative. Intravenous cholecystograms were interpreted as showing a poorly functioning gall bladder.

The patient appeared to be exaggerating his symptoms. Although mesenteric thrombosis was considered as a possibility, the long duration of symptoms appeared to make it unlikely and a tentative diagnosis of subacute cholecystitis was made. The patient expired suddenly on the ward, 3 days after admission to the hospital. Until a few hours before death no significant changes in the physical examination was noted.

Postmortem examination showed vascular occlusion involving the celiac axis, superior and inferior mesenteric arteries. Almost the entire small bowel and part of the large bowel were gangrenous. There were about 250 cc. of bloody fluid in the abdomen and there was a thin, fibrinopurulent exudate scattered throughout the peritoneum. The thrombotic process was an old and progressive one. The superior mesenteric artery had apparently been completely occluded at one time and had been recanalized. The occlusive process in the inferior mesenteric artery also showed evidence of recanalization. There was a fresh thrombus completely occluding the celiac axis artery. Microscopic examination confirmed the impression that the process had been going on for a considerable length of time. There was slight cardiac hypertrophy but no coronary sclerosis or valvular disease. The gall bladder, stomach, duodenum and kidneys showed no variation from the normal.

An evaluation of the clinical and pathologic evidence in this case leads one to the conclusion that a gradual occlusion of the mesenteric arterial system by progressive thrombosis was the cause of recurrent abdominal pain of 2 months' duration. Certain characteristics of this pain merit further consideration. First, although severe it was not sharply localized, did not radiate, and was not associated with muscular spasm or exquisite tenderness of the abdominal wall. Secondly, it was in the beginning, definitely related to the ingestion of food and only later became constant. On the basis of these characteristics the following hypothesis is submitted: Vascular pain in the abdomen is the result of an anoxemia of the intestinal wall and is a true visceral pain manifested through sensory neurones in the sympathetic nerves independently of the musculocutaneous pathways.

At the present time there are two major theories of the nervous mechanism for abdominal pain. One, the Mackenzie theory,³ holds that true visceral pain does not occur but that impulses arising in

diseased viscera (in themselves insensitive to pain) pass by way of the sympathetic nerves, to the cord where they established an "irritable focus" and overflow into the specialized somatic pain tracts. Pain is thus referred to the peripheral somatic nerve endings in the area where the spinal overflow occurs. The other theory proposed by Morley¹ maintains that true visceral pain is conducted by sympathetic pathways directly to the brain independently of the somatic nerves. According to this conception, true visceral pain is not well localized and is not associated with rigidity or exquisite tenderness of the abdominal wall. Only when the parietal peritoneum is irritated and somatic nerve trunks are stimulated is the pain of diseased viscera well localized and associated with muscular rigidity ("peritoneo-muscular reflex"). Recently, interest has been aroused in the old conception that sensory neurones of somatic type exist, although in smaller numbers than is found in the skin, in the mesentery and elsewhere within the abdomen. Heinbecker, Bishop and O'Leary⁴ have shown that sympathetic trunks contain myelinated fibers whose histologic structure and electrical conduction properties are identical with the peripheral sensory pain fibers, and Sheehan⁵ has shown that the myelinated neurones of the Pacinian bodies in the mesentery travel with the sympathetic nerves. In view of these studies it is quite probable that the somatic nervous system is involved in the production of intraabdominal pain.

There is considerable clinical evidence to support this concept of two independent pathways for abdominal pain. One, over sensory neurones that travel in the sympathetic trunks, causing pain which is not well localized, is non-radiating, and is not associated with muscle spasm or severe tenderness, and the other, over the cerebrospinal nerves that supply the parietal peritoneum, causing board-like rigidity and exquisite tenderness ("peritoneo-muscular reflex" of Morley). Thus the early pain of appendicitis is supposed to be a true visceral pain, while the late pain in the right lower quadrant, associated with marked tenderness and muscle spasm is due to direct irritation of the parietal peritoneum. Zollinger⁶ has shown that distention of the gall bladder and common duct in conscious patients although causing considerable distress, does not reproduce the typical pain of biliary colic. He suggests that in true gall bladder colic there is an irritation of the parietal peritoneum, which accounts for the radiation of the pain to the back. The recent studies of Rivers⁷ also lend support to Morley's hypothesis. From a group of cases in which direct examination of the tissues was made and an accurate history obtained he found that the pain of uncomplicated peptic ulcer is poorly localized, but if there is penetration of the ulcer it becomes sharply localized. Rivers concludes that the pain of uncomplicated ulcer is a visceral phenomenon manifested through the splanchnic nerves and that the localization of the pain in penetrating ulcer is due to stimulation of cerebrospinal nerves.

According to Ryle⁸ distention of the hollow viscera is the usual cause of true visceral pain but the occurrence of severe pain without rigidity or exquisite tenderness in the case reported here is evidence that non-fatal or early mesenteric arterial thrombosis is capable of causing the same phenomenon. The exact mechanisms involved in the production of vascular pain are not definitely established. Sutton and Lueth⁹ have produced evidence to show that the pain of angina pectoris is due to anoxemia of the cardiac musculature and Sir Thomas Lewis¹⁰ believes that the pain of intermittent claudication is attributable to metabolites that accumulate in a functioning muscle inadequately supplied with blood. The intermittent character of the pain and its definite relation to the ingestion of food, in the case reported above, suggests that a similar factor may be the cause of vascular pain in the abdomen. The partially occluded vessels, although adequate for viability of the bowel, were unable to meet the increased demand for blood necessary for function and a relative ischemia of the bowel occurred exactly as in the arteriosclerotic leg that is overexercised. Later on as the thrombosis progressed the circulation became inadequate even for the requirements of the bowel at rest. This was manifested clinically by persistence of the pain. Finally gangrene resulted in peritonitis and death.

The clinical importance of vascular pain in the abdomen lies in the fact that it may be the precursor of fatal mesenteric vascular occlusion and a proper appreciation of its characteristics is of great importance in the early recognition of this highly fatal condition. As seen in the reported case, the pain that occurs early in this condition differs from simple vascular pain only in its constancy. It also has the characteristics of true visceral pain as it is not associated with muscular spasm or exquisite tenderness until peritonitis has been established. In a previous communication¹¹ this contrast between the severity and persistence of the pain and the paucity of physical findings was pointed out as one of the most significant diagnostic features of mesenteric vascular occlusion. Recently, we have had an opportunity to confirm these impressions in the case of a young man with rheumatic heart disease who had an embolic occlusion of the superior mesenteric artery. There was severe pain with only moderate tenderness and no rigidity. At operation a few hours after the onset of the pain the bowel was found to be contracted, grayish in color, but not yet gangrenous and there was no evidence of peritonitis. No line of demarcation could be made out so closure without resection was done. During the next 48 hours there was no definite change in the physical findings but the patient appeared definitely worse and at a second exploration the entire small bowel was found to be infarcted but not yet gangrenous and peritonitis had not yet developed. However, the operator felt that the lesion was too extensive to permit resection and the abdomen was closed without drainage. Although masked by liberal doses of morphin, definite signs of peritonitis, characterized by distention

and muscular spasm later developed and autopsy revealed gangrenous bowel and peritonitis. The superior mesenteric artery had been occluded at its base by an embolus. This lack of spasm and exquisite tenderness in the early stages of mesenteric vascular occlusion is in striking contrast to the boardlike rigidity of perforated ulcer or acute pancreatitis and constitutes a valuable diagnostic feature of the condition.

Summary. Evidence is presented to show that vascular disease of the mesentery can cause abdominal pain in the absence of gangrene or peritoneal irritation. It is suggested that pain so caused is the result of an anoxemia of the intestinal musculature, and is a true visceral pain conducted by sensory neurones in the sympathetic nerves independently of the musculocutaneous pathways. The importance of recognizing the characteristics of this type of pain in the early diagnosis of mesenteric vascular occlusion (arterial) is emphasized.

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VASCULAR CHANGES IN INTERMITTENT CLAUDICATION.

WITH A NOTE ON THE VALUE OF ARTERIOGRAPHY IN THIS SYMPTOM COMPLEX.

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ALTHOUGH intermittent claudication has been recognized for many years as a possible concomitant of peripheral vascular disease, many phases of the condition are still obscure and little under-

stood. For one thing, it is a very inconstant phenomenon, and its presence seems entirely unrelated to the type of vascular disease with which it is associated, or to its degree. It frequently is evident in patients whose disease process never passes beyond the initial stage, and it is just as frequently absent in others who exhibit terminal gangrene. Again, the origin of the pain of intermittent claudication has never been satisfactorily explained, and even the most logical theory, as we shall point out shortly, is still largely hypothetical. Finally, so far as we are able to ascertain, the pathologic changes of intermittent claudication have never been described *in vivo*, though they have been thoroughly studied in the laboratory and at the postmortem table. With the second and third of these considerations, and more particularly with the third, this present communication is concerned.

The various theories advanced to explain the pain of intermittent claudication have been excellently summarized by Lewis, Pickering and Rothschild,¹ in a valuable communication in which are set forth also the results of their own experiments in this field. Charcot,² they point out, believed that the basis of the pain is a muscular cramp, comparable to the so-called "cadaveric rigidity," which is the result of a deficient blood supply to the parts. Marinesco,³ arguing along the same lines, advanced the idea that the cramp occurs because the blood supply to the muscles is inadequate during exercise, although it is entirely adequate during rest. Goldflam and Erb,² although they accepted the theory of muscular cramp, admitted the possibility of other extramuscular structures, such as the arteries or even the skin, being the seat of the pain.

But muscular cramp, as Lewis and his co-authors point out, and as every careful observer knows, although it may be associated with intermittent claudication, is by no means a constant concomitant and is by no means essential to its production. We would suggest, as an interpolation of our own, that perhaps the theory of muscular cramp arose originally merely because the usual patient, hampered by the difficulty of translating his discomfort into words, used the term "cramp" to describe his pain. Other theories have arisen on no sounder foundation.

Kissin's² theory, that the cause of exercise pain is an anoxemia produced in the muscles from an obstruction of the arterial blood supply, is disproved, Lewis and his associates point out, by their own observations. They were able to show that obstruction of the vessels before exercise, even for 10-minute periods, does not initiate the pain, and that continuation of the obstruction after the exercise pain has reached its acme does not aggravate it. Furthermore, they showed by repeated tests in the same individual that the pain does not occur at all if the exercise is discontinued just before the pain is anticipated, though at this time the "oxygen debt" would supposedly be at its height.

The theory of arterial spasm was first suggested by Erb,² who did not believe that mechanical narrowing of the bloodvessels was sufficient to explain the whole picture, and it has been championed since by other observers, notably by Zak.² But Lewis and his co-authors, while granting the truth of Zak's observations, are unwilling to accept them in their universal application. Zak's theory is based on the following experiment: After the circulation was shut off, the patient was required to open and close his hand energetically until, usually at the end of 30 such movements, the fingers became white and cool and exercise pain appeared. The circulation was then released. In all of Zak's observations the blood did not return to the fingers for several seconds, sometimes as long as 10 seconds, the delay, in his opinion, being evidence of vascular contraction. Lewis³ grants that the contraction is present, but is unwilling to grant that it is due to spasm; he explains it by the fact that the fingers have become cold during the exercise, and that cold always contracts the digital arteries. When he and his associates made the same observations with the fingers warmed, they found that the pain still occurred, but that there was rarely any delay in the return of the circulation to the hand, just as there was no appreciable delay in its return to the control hand if it were similarly warmed but not exercised. Lewis explains the few cases in which, after the release of the obstruction, there was a delay in the return of the circulation to the exercised hand, by the diversion of the blood to the greatly dilated vessels of the muscles of the forearm.

The theory which Lewis and his co-workers have advanced to explain the pain of intermittent claudication is based on an elaborate set of experiments dealing with the production of ischemic pain by obstruction of the arterial supply. On the basis of these experiments they conclude that the pain is caused by a product of muscular metabolism, which they term factor P. The background, so to speak, is an inadequate blood supply to the muscles of the parts, the inadequacy being evident only during exercise. When successive muscular contractions occur, the state of the muscle undergoes a progressive alteration, and as this alteration takes place, its product, the hypothetical factor P, is given off and collects in the extramuscular tissue spaces. Factor P, which is a physico-chemical product with a cumulative action, is given off during exercise, they believe, even when the blood supply to the muscle is adequate, but under those circumstances it does not rise to the pain level in the tissue spaces. In other words, although obstruction to the blood supply is the essential basis of the pain, the pain stimulus itself, the hypothetical factor P, is a product given off by the muscle fibers. The theory is ingenious, but obviously, until factor P has been isolated, it must remain only a theory.

Our present communication is based on the study by arteriog-

raphy of 15 carefully selected cases of intermittent claudication which have been observed during the last 3 years. Fourteen patients were male and 1 female, 12 were white and 3 colored, but this distribution, in so small a number of observations, probably has no particular significance. The age range was from 23 to 77 years; 4 patients were between 30 and 40, 3 between 40 and 50, 5 between 50 and 60 and 3 over 60. The duration of symptoms varied from 2 months to 4 years.

All of these patients had perfectly typical histories, which, in a composite form, were about as follows: The first symptom noted was a sense of fatigue after walking, sometimes in one leg, more usually in both, and always eventually in both. By slow degrees this sense of fatigue passed over into actual pain, which, by equally slow degrees, increased in severity; it was always confined to the calf muscles. At first it was noted only after a long walk, then it began to occur after shorter and shorter walks, and finally it occurred, with great severity, after a walk of only a short distance, sometimes only a few hundred feet. At first it was relieved by rest, but longer and longer intervals of rest became necessary to relieve pain which occurred after shorter and shorter walks, and finally the patient was for all practical purposes physically incapacitated. The pain was usually described as a cramping or drawing sensation in the muscles of the calf, and it naturally varied in the individual patient in its duration and severity, and in the amount of exercise necessary to produce it.

In 12 cases the etiologic basis was definitely arteriosclerotic, and the patients in this group, in addition to intermittent claudication, exhibited other evidences of arteriosclerotic disease, chiefly beading of the arteries, absence of the dorsalis pedis pulse, pallor and coldness of the extremities, exaggeration of the pain on exposure to cold, and night pain of varying degrees of severity. In the remaining 3 cases, which will be discussed later in detail, the etiologic basis could not be definitely determined. In all 15 cases syphilis was not a factor, and Buerger's disease was also eliminated, in order that the vasospastic and inflammatory phenomena characteristic of it should not confuse the picture.

These 15 cases were studied by means of arteriography of the regional blood supply with stabilized thorium dioxide (Thorotrast Heyden). This agent, as we have pointed out in other communications,^{4,5,6} is an opaque substance admirably adapted for visualization of the vascular tree. It has no perceptible effect on the diseased vessels, it is non-toxic in the dosage necessary for the purpose, and in an experience of almost 3 years, in over 300 cases, we have noted no deleterious effects from its use.

In all instances the pain of which the patients in this series complained was confined to the muscles of the calf, and for purposes of comparison it was, therefore, necessary to establish the

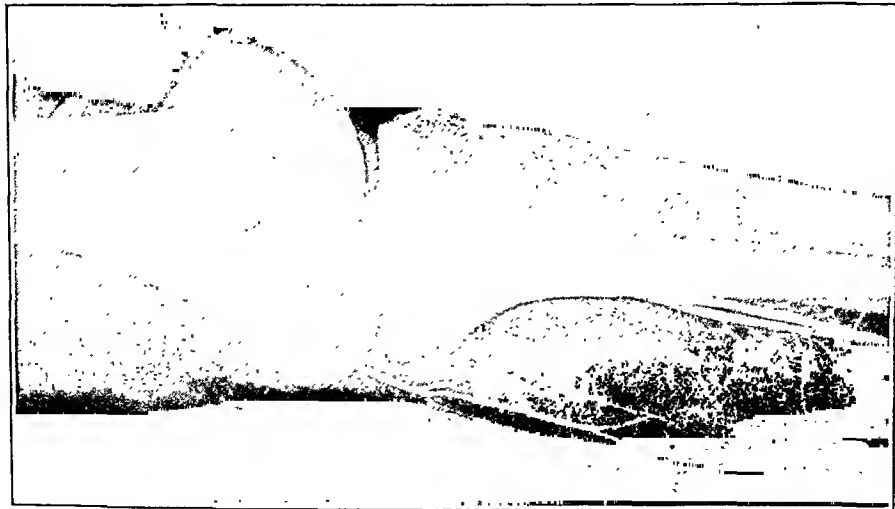


FIG. 1.—Normal vascular supply of the popliteal region in a white male, aged 45 years.

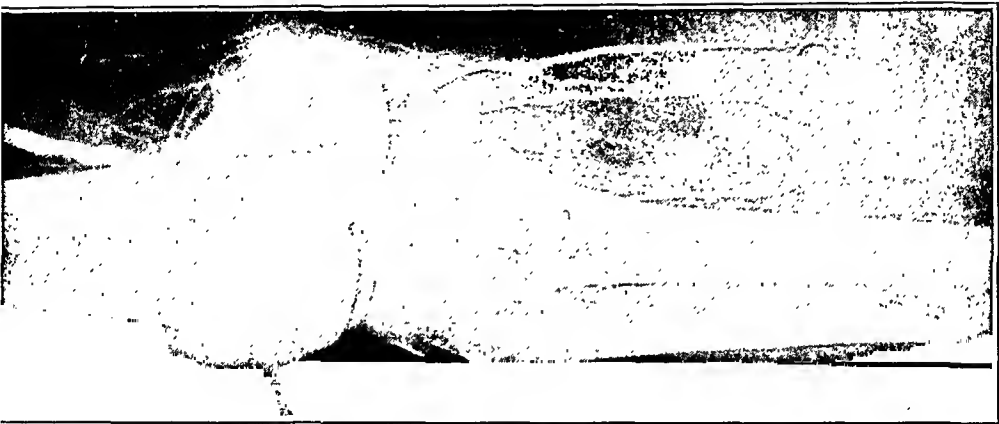


FIG. 2.—Complete obliteration of the popliteal artery, with narrowing of the tibial vessels, in a case of intermittent claudication. Note the lower caliber of the vessels.

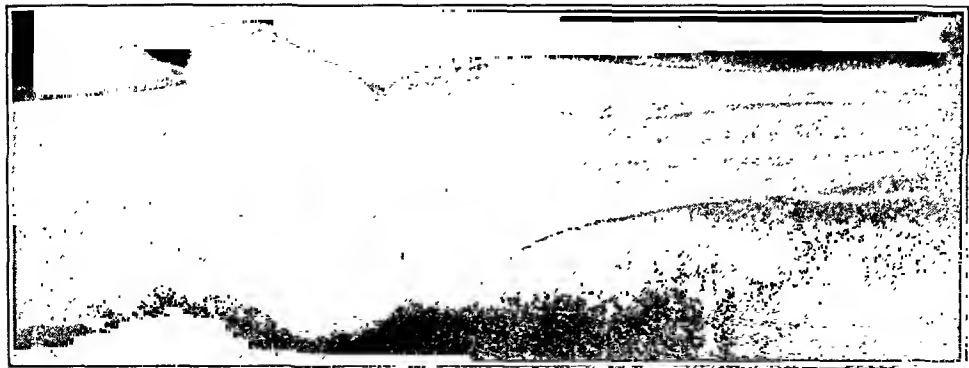


FIG. 3.—Marked narrowing of the femoral, popliteal and tibial vessels in a case of intermittent claudication. Note the reduction in caliber.

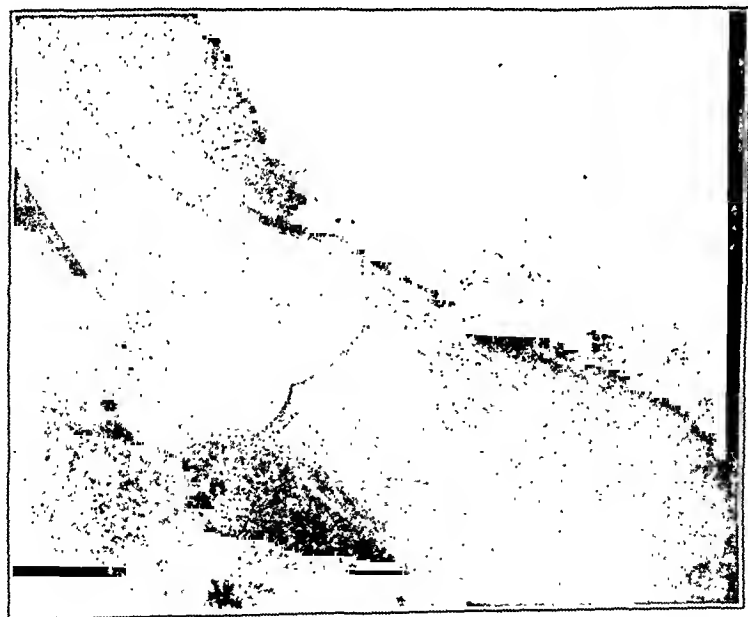


FIG. 4.—Intermittent claudication of undetermined origin. Note the peculiar dilatation and clubbing of the muscular branches, the marked narrowing of the popliteal artery, and the numerous small collateral vessels.

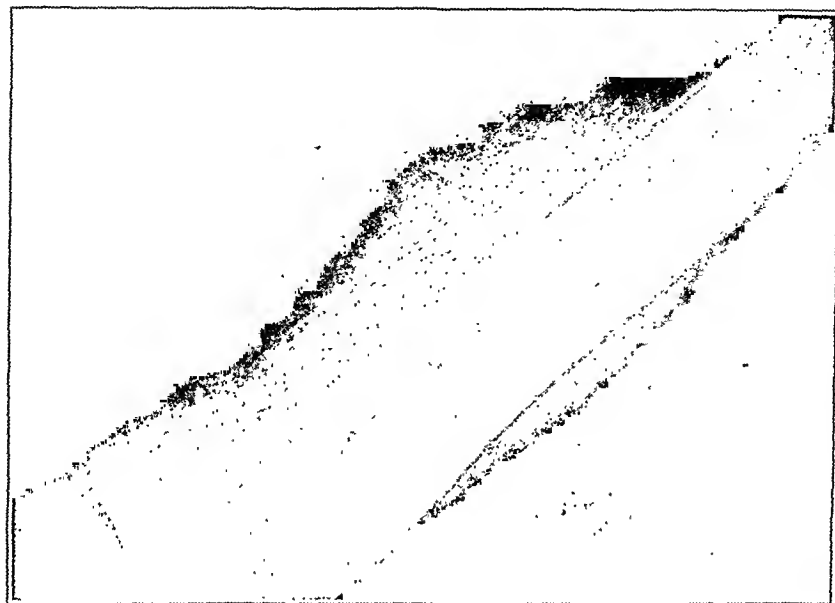


FIG. 5.—Blood supply of the popliteal region during rest in a case of intermittent claudication. Note the narrowing of the popliteal artery and the obstruction of the anterior tibial artery.

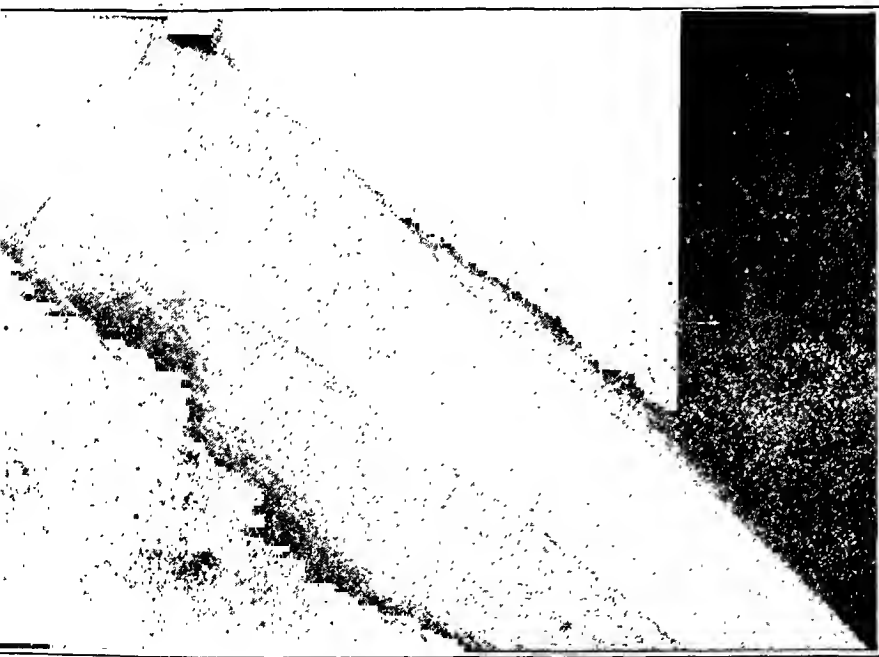
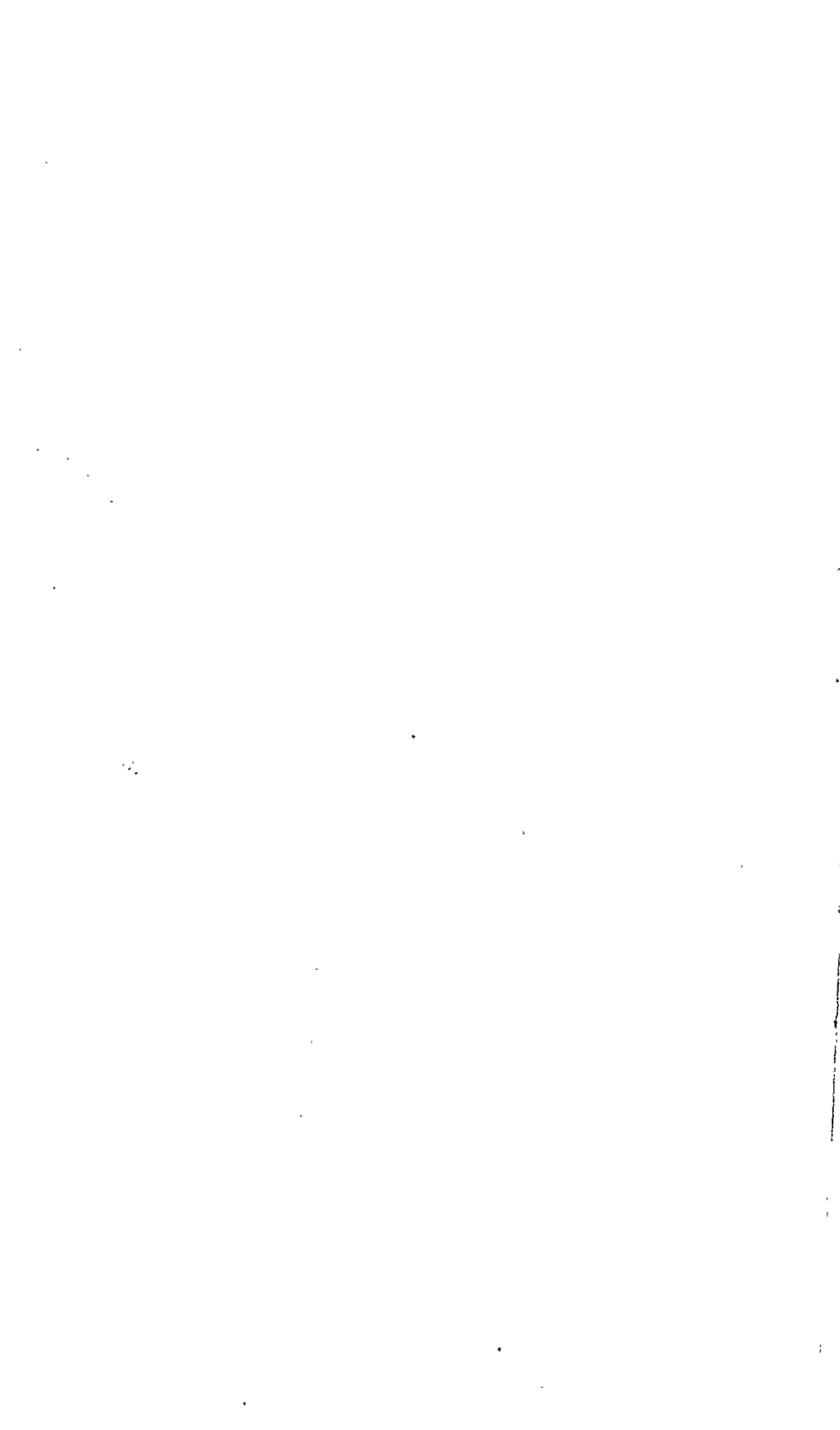


FIG. 6.—Blood supply of the popliteal region during exercise pain in the case of intermittent claudication shown in Fig. 5. Note the dilatation of the larger vessels and the presence of numerous fine vessels not visualized during life.



FIG. 7.—Arteriography 14 months later, after treatment, in the case of intermittent claudication shown in Fig. 2. Note the slight increase in the size of the large arteries and the more marked increase in the number of small branches supplying the soft parts.



normal picture of the regional blood supply. Repeated observations have established the following criteria, which can be noted in Fig. 1.

1. The femoral, popliteal and tibial arteries are smooth and regular in their course, without narrowing of the channel at any point by plaques or other obstructions.
2. The large muscular branches are long and evenly distributed.
3. The small muscular branches are numerous and are given off at regular intervals from the larger branches. They terminate in fine twigs, which, in turn, supply even finer twigs to all parts of the soft tissue.

On the basis of the hallmarks of the normal vascular supply, namely, smoothness of contour, regularity of pattern, and adequacy of size and distribution, we studied the arteriographs of these patients with intermittent claudication. In addition, we noted particularly the size and distribution of the collateral circulation. Our experience with arteriography in various types of peripheral vascular disease has made us aware of the fact that the collateral circulation, however efficient it may be, cannot possibly be as efficient as the normal circulation because it practically never reaches all of the smaller muscular fibers. It should be stated that all of the arteriographs, except when otherwise specified, were taken during the rest period.

The arteriographs fall into 3 distinct groups. In the first group (6 cases) the etiologic basis was arteriosclerosis, and the most outstanding change was obliteration of the large arteries. In 3 cases the obliteration involved only the popliteal artery (Fig. 2), in 2 it involved the tibial vessels just below their point of origin and in the remaining case it involved the popliteal and lower femoral arteries. In the cases in which the tibial vessels were obliterated the popliteal vessels were markedly narrowed, just as in those cases in which the popliteal vessels were obliterated, the tibial vessels were markedly narrowed. In all 6 cases in this group there was a diminution in the number of the large muscular branches, and their distribution was uneven and clearly inadequate. The 4 cases in which the popliteal artery was completely obliterated showed many new collateral vessels, which were, however, inadequate in their distribution.

In the second group (6 cases) the etiologic basis was again arteriosclerosis. In these cases the large arteries were not obliterated, but the lumen was markedly narrowed (Fig. 3), especially in 3 cases in which the encroachment of plaques caused definite areas of constriction. In this group also there was a marked diminution in the size of the muscular branches and in the number of the finer muscular terminals. In the 3 cases in which plaques were not present, the main pathologic change was confined to the large and small muscular branches, which were so reduced, both in number

and size, that in only a few areas did the vascular pattern approach the normal; in other areas there were few visible branches and sometimes none at all. In all 6 cases in this group the new collateral blood supply was frankly inadequate.

The most important vascular changes in these first two groups, then, included in one group obliteration of the large arterial trunks and in the other more or less diminution in the size of the lumen of the arterial trunks, and marked diminution in both the size and number of the large and small muscular branches. The collateral blood supply, although apparently adequate in the number and size of its branches, was practically always inadequate in distribution.

The last group includes the 3 patients in whom no etiologic basis for the intermittent claudication could be discovered. All 3 of them gave a history of some prolonged febrile disturbance of unknown origin in early adult life; in 2 cases this illness was associated with pain in the extremities, and can be assumed to have initiated the vascular disturbance.

The first patient, who showed the least marked variation from the normal on radiographic study, had, curiously, the most acute symptoms. He was a negro male, aged 23 years, who came into the hospital complaining that he could walk only a few feet without pain. Even at rest he had pain, which was increased by palpation, in the calf muscles and the toes. The dorsalis pedis pulse was palpable bilaterally, and there were no gross changes in the extremities. There was no febrile reaction. Arteriographic study showed a peculiar clubbing and dilatation of the muscular branches, which terminated very abruptly. No change was evident in the main arteries.

The second patient was a white male, aged 40 years, who gave a typical history of bilateral intermittent claudication after walking two blocks. The dorsalis pedis pulse could not be made out. Arteriography showed the same peculiar configuration of the muscular branches described in the first case, which was associated with a narrowing of the popliteal and tibial arteries (Fig. 4).

The third patient, a white male, aged 46 years, complained of the same symptoms and exhibited the same type of vascular damage already described, except that in this case the process included the popliteal artery, which was completely obliterated.

We have, then, a group of 3 successively older patients, in each of whom successively more serious vascular changes are exhibited. All the evidence goes to prove that the process, whatever it may be, begins in the muscular branches, which are typically short and clubbed, and finally progresses to the large arteries, which eventually are completely obliterated. We might add that, although we have not secured biopsy specimens from any of these patients, such an investigation should certainly be undertaken in an endeavor further to elucidate this curious pathologic picture.

Lewis' experiments, as we have already mentioned, eliminate arterial spasm as the cause of the pain of intermittent claudication; indeed, he was able to show that immediately after the release of the vascular obstruction, and while ischemic pain is still felt, the blood supply to the parts is increased, sometimes 20 times over the resting circulation. We have been able to corroborate his observations by the following tests upon a patient with intermittent claudication:

A white male, aged 46 years, told a typical story of intermittent claudication produced by walking two blocks. After a prolonged rest period he was lifted from a rolling chair to the Roentgen ray table. Arteriography at this time (Fig. 5) showed a marked narrowing of the popliteal artery, with obstruction of the anterior tibial artery at several points, and a marked diminution in the size of the muscular branches. There was evidence of a newly formed collateral circulation. Two days later this patient was made to walk until the pain in his calf muscles had completely incapacitated him; after he was allowed to rest, it was fully 5 minutes before the pain began to disappear, and it persisted in a milder form for 5 or 6 minutes longer. Following another long period of rest, he was again made to walk until he was incapacitated; then, with as little delay as possible, he was lifted to the Roentgen ray table and another arteriogram was taken. The whole procedure consumed not more than $1\frac{1}{2}$ minutes, and the intense pain persisted, as at the first test, for more than 5 minutes. This arteriogram (Fig. 6) showed an increase in the size of the arterial lumen, some enlargement of the muscular branches, and the visualization of numerous fine branches not seen in the first picture.

This observation, therefore, bears out Lewis' contention that the blood supply to the extremity is increased rather than decreased at the height of the pain, and furnishes at least indirect support to his theory that some physicochemical change in the nutrition of the muscles is the cause of the pain. The theory is further supported by the fact that in all 15 of our cases some distinct change can be made out in the nutrition of the muscles. In some instances the change was in the muscular branches alone, in others the principal change was in the large arteries and the muscular branches were only secondarily affected, but always the arteriographic evidence supported the theory that impairment of the muscular nutrition was the basis of the pain.

Some of the patients in this series we have been able to study over many months, and successive arteriograms have proved very interesting. One of these cases might be mentioned in detail, for it proves very clearly that intermittent claudication is really a blessing in disguise, in that it forces patients, because of their pain, to seek medical advice far earlier than they would otherwise. The intensity of the pain, furthermore, and the resulting incapacitation make them unusually coöperative.

A white male, aged 72 years, entered the hospital 14 months ago complaining of pain in both calves after walking even half a block. Four months before admission he had begun to have a drawing sensation in the calf muscles of both legs after walking any considerable distance. This discomfort gradually merged into pain, and when he was first observed he could walk only a few hundred feet without stopping to rest. He exhibited the typical signs of arteriosclerosis, including a bilateral absence of the dorsalis pedis pulse, he had severe night pains and all his symptoms were aggravated by exposure.

Arteriography at this time (Fig. 2) showed a complete obliteration of the popliteal artery at its middle portion, and a marked narrowing of the femoral artery, which was constricted at several points by the encroachment of large plaques upon its lumen. The blood supply of the calf muscles was from a large branch from the lower third of the femoral artery, which passed below the knee and terminated at the junction of the upper and middle third of the leg, and from 3 large branches of the popliteal artery, which arose just above the point at which it was obliterated and which descended well down into the leg. The number of large and small muscular branches was apparently adequate, but their distribution was not, and it was apparent that many areas had a poor blood supply or none at all.

This patient was treated intensively with diathermy, contrast baths, hot baths twice a day, and vascular exercises so graded that they stopped just before pain was precipitated. At the end of 3 months, although he still noted a sense of fatigue in his calf muscles, he was able to walk several blocks in comparative comfort. The arteriogram at this time practically duplicated the first picture. Now, at the end of 14 months, he can walk 25 blocks without pain. He begins to feel fatigued at the end of 12 or 14 blocks, but he can walk, more slowly, almost twice as far. His night pain, although less troublesome, still persists. Arteriography at this time (Fig. 7) still shows little change from the original picture; there is a slight widening of the tibial vessels, some enlargement of the large branches of the popliteal artery, and perhaps a slight improvement in the collateral circulation, particularly in the very fine branches.

Quite evidently the improvement in the blood supply is not enough to explain this patient's clinical improvement. Our interpretation of the change in his symptoms is that the regional blood supply, at least for several hours each day, is so much increased by heat and exercise that the hypothetical factor *P* of Lewis does not reach the pain level. It may be, too, that the temporary improvement in the nutrition of the parts actually alters the physicochemical changes which occur as the result of exercise. Whatever the explanation, there is no doubt that the patient has improved. He has been tided over the crisis that, without treatment, might have terminated in irremediable disease, and the chances are that even

if no further improvement occurs, there will be no further extension of his disease.

One other point should be noted, that arteriography is a valuable means of making a differential diagnosis in obscure cases of pain in the extremities in which the vascular lesions are not evident grossly. Such cases are frequently diagnosed as arthritis, neuritis and other extravascular conditions, and the golden opportunity is lost of arresting the disease as it was arrested in the patient whose history we have just outlined.

Summary. 1. The theories of the origin of pain in intermittent claudication are briefly reviewed.

2. An arteriographic study of 15 carefully selected cases of intermittent claudication is reported.

3. Attention is called to the fact that in 3 cases of undetermined etiology the radiographic evidence shows an entirely different type of lesion from that noted in the other 12 cases, in which the etiology was arteriosclerotic.

4. Arteriographic evidence is adduced to support the contention that the pain in intermittent claudication is not due to arterial spasm.

5. An illustrative case is cited to show that the improvement which follows heat, exercise and similar measures in intermittent claudication is not due to any notable change in the vascular supply but presumably to the temporarily increased nutrition of the parts which is achieved by this form of therapy.

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BOOK REVIEWS AND NOTICES.

CLINICAL MISCELLANY, Volume 2, 1935. *The Mary Imogene Bassett Hospital, Cooperstown, N. Y.* By 9 Contributors. Pp. 218; illustrated. Baltimore: Charles C Thomas, 1935. Price, \$3.00.

THIS volume comprises 20 papers by 9 contributors from the Bassett Hospital, the majority, case reports. In general the cases are well selected and the study that each case has received reflects much credit on the Hospital as well as on the individual authors. From the standpoint of the general reader, Volume II represents a decided advance over its predecessor in that more of the papers deal with series of cases instead of with single occurrences of very rare conditions. The new volume is further improved by a number of excellent illustrations and by frequent brief discussions of the literature which serve to orient the reader if he is unfamiliar with the field. Of particular interest were the epidemiological study of poliomyelitis in a rural community by F. F. Harrison and M. F. Murray, the paper on post-vaccinal polyneuritis by F. F. Harrison, a study of Bacteremia based on over 1200 blood cultures by G. M. Mackenzie and R. M. Pike, and the report of a case of fatal hemorrhage complicating scarlet fever by M. F. Murray.

J. R.

A MANUAL OF THE COMMON CONTAGIOUS DISEASES. By PHILIP MOEN STINSON, A.B., M.D., Assistant Professor of Clinical Pediatrics, Cornell University Medical College; Visiting Physician, Willard Parker Hospital, etc. Pp. 437; 53 illustrations and 3 plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$4.00.

PRACTITIONERS and students will welcome the new edition, enlarged and thoroughly revised, of this practical, well-written, handy little volume that testifies to the author's clinical and teaching experience. R. K.

GRUNDZÜGE DER PRAKTISCHEN SEELENHEILKUNDE. By DR. MED. FRITZ KÜNKEL, Berlin. Pp. 168. Stuttgart: Hippokrates Verlag. Price, Rm. 6.75, paper binding; Rm. 8, linen binding.

A PRACTICAL text for the general practitioner. The author points out that the increasing complexity of psychiatry has been increasingly confusing to the general practitioner, yet he is the one who is particularly in need of knowledge of the subject, since in his daily practice he is the first to encounter the numerous psychiatric problems in their inception. Just as books are written on "minor surgery" to meet the needs of the general practitioner, so in this instance the author places his emphasis largely on "minor psychiatry" (although some of the illustrative case material is decidedly "major"). The book will make interesting and profitable reading for all clinicians with a knowledge of German. R. K.

YOU MUST EAT MEAT. Fancies, Foibles and Facts About Meat. By MAX ERNEST JUTTE, M.D., Formerly Lecturer on Stomach and Intestinal Diseases, New York Polyclinic Medical School, etc. Pp. 164; illustrated. New York: G. P. Putnam's Sons, 1936. Price, \$2.00.

A TIMELY book presenting in readable fashion the case for a well-balanced diet. It is an authoritative criticism of the present tendency toward over-indulgence in "rabbit food." W. J.

LE SANG DES HYPERTENDUS. By GEORGES CARRIÈRE, Professor of Clinical Medicine, and CLAUDE HURIEZ, Chief of the Medical Clinie at the Faculty of Medicine of the University of Lille. Pp. 386; 53 tables. Paris: G. Doin et Cie, 1936. Price, 50 fr.

THIS work comprises a study of the physieal and chemieal characteristics of the blood in the presenee of arterial hypertension. It is based upon the published reports of the authors and their co-workers of some 2000 determinations made in a series of 105 selected eases.

Hypertension is elassified according to whether it oecurs as an isolated phenomenon, is complicated by other disease or is simply associated with other disease. Although the blood pattern is somewhat different in these 3 groups, it seemed to the authors of greatest interest that there was a eonsistent alteration of the lipoids and proteins, together with an increase in osmotic pressure. These ehangs they regard as intermediary between the hypertension and a widespread metabolic disorder, essentially endocrine in background and involving especially the adrenals, thyroid and liver.

The book contains excellent tables presenting all data made in the course of the authors' study. It includes also a fair review of current opinion on the subject, together with a bibliography of 800 references, predominantly French. It is, in short, a complete expression of the authors' views on the alterations of the blood in hypertension and may therefore be recommended as being of interest to investigators in this field. L. L.

LOBAR PNEUMONIA AND SERUM THERAPY. With Special Reference to the Massachusetts Pneumonia Study. By FREDERICK T. LORD, M.D., Clinical Professor of Medicine, Emeritus, Harvard Medical School, etc., and RODERICK HEFFRON, M.D., Field Director, Pneumonia Study and Service, Massachusetts Department of Public Health. Pp. 91; 10 figures and 1 plate. New York: The Commonwealth Fund, 1936. Price, \$1.00.

THIS handbook deals with lobar pneumonia and its treatment with serum. It discusses the Neufeld technique for the rapid determination of the pneumococcus type, the technique and results of serum administration, and serum reactions and their prevention.

This brief work, written in the light of the Massachusetts pneumonia study, should prove decidedly helpful to praetitioners who are interested in lowering their mortality by the use of serum. J. A.

ATLAS OF PATHOLOGICAL ANATOMY, Volume 2. Compiled by E. K. MARTIN, M.S., F.R.C.S. Issued under the Direction of the Editorial Committee of the British Journal of Surgery. Pp. 475; 268 illustrations (168 in colors). Baltimore: William Wood & Co., 1935. Price, \$15.00.

THIS second volume continues the method of presenting gross pathology and the high standard of the first. All of the illustrations are life-like yet accurate, and eonsiderably more than half in well reproduced colors. This last item in itself would make the price prohibitive if the book had been printed in this country, rather than in England. The 55 sections of this volume eover lesions of the joints, fibroeystic disease of bone, the thyroid the gastro-intestinal traet, the bladder and male genital tract, and a few miscellaneous conditions. Most of the illustrations are full page, with a description and points from the clinical history on the opposite page. As an adjunct to the study of actual lesions in the museum, or better at the autopsy table when possible, this book should be valuable to graduate and undergraduate students as well as to praetitioners who attempt to keep their knowledge of pathology fresh and useful. E. K.

AMERICAN CHAMBER OF HORRORS. *The Truth About Food and Drugs.* By RUTH DEFOREST LAMB. Pp. 418; illustrated. New York: Farrar & Rhinehart, 1936. Price, \$2.50.

"THE book points out the abuses in the cosmetic industry that flourish because the Federal Government has no control over beauty preparations, however harmful they may be; reveals the jokers in the present law that prevent the carrying out of its original purpose as respects both food and drugs; shows how and why the Government is powerless to do anything about abuses which have grown up since the Wiley law was enacted; shows the rackets that flourish because there is no control of advertising; tells the inside story of the Food and Drug Administration's fight to protect consumers against poisonous spray residue—the first time it has ever been told; takes the lid off the butter industry and exposes incredible conditions, showing how and why they exist and how they could be corrected; tells how the farmers are swindled with veterinary frauds; gives glimpses behind the scenes in an exciting but unpublicized Government agency that the public really knows very little about; indirectly shows the kind of men in charge of enforcement; though it is not official, could not have been written by anyone outside the Government." (From the Publishers' jacket.)

GASTRITIS AND ITS CONSEQUENCES. By KNUD FABER, M.D., LL.D., ENG., F.R.C.P., ENG., HON., Professor of Internal Medicine in the University of Copenhagen. Pp. 119; 48 illustrations. New York: Oxford University Press, 1935. Price, \$3.00.

"THE wheel is come full circle." A generation ago, "gastritis" was a diagnosis frequently made. But with the introduction of Roentgen rays and increasing surgical exploration of the stomach, "gastritis" gave way to organic (ulcer) or functional (gastric neurosis) diagnoses. But once again, newer knowledge of disease (*e. e.*, pernicious anemia) and newer methods of study (*e. g.*, gastroscopy) have reclaimed "gastritis" from its near-oblivion and placed it in a higher and more significant place than ever. The chapter headings tell the story: Acute and Chronic Gastritis (Normal Appearance of the Stomach); Gastritis and Hyperacidity (Pyloric Gastritis, Gastritis as the Cause of Ulcer); Gastritis and Anacidity (Gastritis and Pernicious Anemia). The author is eminently qualified to present the subject, for his researches have played a most important rôle in its development. All clinicians will welcome this little volume. R. K.

DELAFIELD AND PRUDDEN'S TEXT-BOOK OF PATHOLOGY. Revised by FRANCIS CARTER WOOD, M.D., Director of the Pathological Department, St. Luke's Hospital, New York; Director of the Institute of Cancer Research, Columbia University, New York. Pp. 1046; 839 illustrations and 22 full-page plates, many in color. Sixteenth edition. Baltimore: William Wood & Co., 1936. Price, \$10.00.

THIS sixteenth edition, appearing 51 years after the first, is put forth as a jubilee edition. As its reviser points out, it was the first important American textbook of pathology after Gross' work (1839), which was practically the first American book on the subject. What a chance to follow the development of pathology during its most important period! But the editor claims to have resisted the pressure to make the new editions more modern on the specious ground that people have the same lesions as earlier, though the names may have changed. Such a policy, to be sure, makes the work more easily available "as a reference work by those long past their student days," who will be more at home with the parenchymatous

and vascular types of chronic nephritis, for instance, than with the later classifications now generally in use. Fortunately, however, the policy has not always been carried out. The section on tumors, for instance—almost 100 pages—makes the best modern presentation of the subject that can be found in a one volume textbook—a result not to be wondered at in view of the editor's eminence in this field. The chapters on the Nervous System, the Muscles, Bones and Joints show extensive changes, and the rich bibliography shows many references of recent date. E. K.

DIFFERENTIALDIAGNOSE IN DER INNEREN MEDIZIN. By PROF. DR. MED. O. NAEGELI, Direktor der medizinischen Universitätsklinik, Zürich. Pp. 216; 55 illustrations, some in colors. Leipzig: Georg Thieme, 1936. Price, M. 9.60.

EMPHASIZING general biological concepts rather than "minor signs which seldom can give anything important to differential diagnosis," this book aims to show the practitioner how to get further help—usually in laboratory methods. Especially in disorders of blood and spleen, that occupy most of this section, does the author feel that this applies. Disease pictures are not given and, while the important differential points are valuable for reference, they seem too much condensed to permit the work to serve as more than a useful adjunct to more complete presentation of the diseases covered. E. K.

AUS MEINEN KRANKENBLÄTTERN. Von der Arbeit eines Landarztes. By DR. AUGUST HEISLER, Sanatorium Luisenrube und Kinderweide Königswald im Schwarzwald. Pp. 68. München: Verlag der Arztlichen Rundschau, Otto Gmelin, 1936. Price, Paper, Rm. 1.58; Bound, Rm. 2.25.

THIS is pamphlet No. 47 of a collection of diagnostic and therapeutic dissertations for the practitioner. It consists of five addresses by the author on topics ranging from case reports of the results of leeching to the dedication of a village water main. R. K.

NEW BOOKS.

Abortion. Spontaneous and Induced. Medical and Social Aspects. By FREDERICK J. TAUSSIG, M.D., F.A.C.S., Professor of Clinical Obstetrics and Clinical Gynecology, Washington University School of Medicine, St. Louis. (This volume is one of a series dealing with medical aspects of human fertility sponsored by The National Committee on Maternal Health, Inc.) Pp. 536; 146 illustrations and 27 tables. St. Louis: The C. V. Mosby Company, 1936. Price, \$7.50.

The Harvey Lectures, Series XXX. Delivered under the Auspices of The Harvey Society of New York, 1934-1935. Under the patronage of the New York Academy of Medicine. By DRs. WM. BOSWORTH CASTLE, WILLIAM CUMMING ROSE, WILBUR A. SAWYER, ALFRED N. RICHARDS, E. C. DODDS, G. V. ANREP, FRANCIS G. BLAKE and JOHN H. NORTHROP. Pp. 270; illustrated. Baltimore: The Williams & Wilkins Company, 1936. Price, \$4.00.

The Adrenals. By ARTHUR GROLLMAN, PH.D., M.D., Associate Professor of Pharmacology and Experimental Therapeutics, and formerly Associate Professor of Physiology in the Medical School of The Johns Hopkins University. Pp. 410; 17 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, \$5.00.

The Common Cold and Influenza. And Their Relationship to Other Infections in Man and Animals. By J. E. R. McDONAGH, F.R.C.S. Pp. 152. London: William Heinemann, Ltd., 1936. Price, 12s. 6 d.

The 1935 Year Book of General Surgery. Edited by EVARTS A. GRAHAM, A.B., M.D., Professor of Surgery, Washington University School of Medicine; Surgeon-in-Chief of the Barnes Hospital, and of the Children's Hospital, St. Louis. Pp. 838; 206 illustrations. Chicago: The Year Book Publishers, Inc., 1936. Price, \$3.00.

This volume, one of ten that has been appearing annually for 35 years, covers the advances in the field of surgery in the past 2 years. Similar volumes appear from the same publishing house on General Medicine; General Surgery; Eye, Ear, Nose and Throat; Pediatrics; Obstetrics and Gynecology; General Therapeutics; Urology; Neurology, Psychiatry and Endocrinology; Dermatology and Syphilology, and Radiology. While most of the matter is classified according to regions of the body, there are also subdivisions on Anesthesia, Asepsis, Operative Technique, Wound Healing and Pathologic Interventions, Tetanus, Malignant Tumors, and Orthopedic Surgery. The book contains a wealth of information, some of it of more statistical than intrinsic value. The chief increases are found in the fields of peripheral vascular and thoracic surgery. American literature does not predominate.

Allergy of the Nose and Parnasal Sinuses. A Monograph on the Subject of Allergy as Related to Otolaryngology. By FRENCH K. HANSEL, M.D., M.S., Assistant Professor of Clinical Otolaryngology, Washington University School of Medicine; Fellow of the Association for the Study of Allergy, etc. Pp. 820; 58 illustrations, 4 charts and 58 tables. St. Louis: The C. V. Mosby Company, 1936. Price, \$10.00.

Lecciones de Patología Médica. Tome 2. By DR. C. JIMENEZ DIAZ. Tomadas taquígraficamente por el Dr. J. DE PAZ MONTALVO. Pp. 1403; 297 illustrations. Barcelona: Editorial Científico Medica, 1936. Price not given.

This second volume, the first not having been received, devotes 156 lectures to the pathologic anatomy and physiology of the kidney, the nervous system, the lungs, the circulatory, and digestive tracts. The first two occupy three-fourths of the total space.

Interpretation of Laboratory Findings. By RAYMOND H. GOODALE, M.D., Pathologist, City Hospital, Worcester, Mass.; Visiting Pathologist, Belmont and Fairlawn Hospitals, Worcester, etc. Pp. 170. Philadelphia: F. A. Davis Company, 1936. Price, \$2.25.

Biological Effects of Radiation. Mechanism and Measurement of Radiation Applications in Biology, Photochemical Reactions, Effects of Radiant Energy on Organisms and Organic Products. Vols. 1 and 2. Prepared under the Auspices of the Committee on Radiation, Division of Biology and Agriculture, National Research Council, Washington. Edited by BENJAMIN M. DUGGAR, Professor of Plant Physiology and Applied Botany, University of Wisconsin, with the coöperation of JANET HOWELL CLARK, KENNETH S. COLE, FARRINGTON DANIELS, GIOACCHINO FAILLA, CHARLES PACKARD and HENRY W. POPP. Pp. 1342; illustrated. New York: McGraw-Hill Book Company, Inc., 1936. Price, \$12.00.

1^{ère} Semaine Médicale Internationale en Suisse. Montreux, 9-14 Septembre, 1935. Organisée par le Journal Suisse de Médecine. Sous le patronage du Haut Conseil Fédéral de la Confédération Suisse. Pp. 477; illustrated. Bale: Benno Schwabe & Cie, 1936. Price, Sw. Fr. 20.

NEW EDITIONS.

The First Decade, 1926-1936. The University of Rochester School of Medicine and Dentistry, Strong Memorial Hospital. Pp. 208; illustrated. Second edition. Rochester, N. Y.: By the University. Price not given.

PROGRESS OF MEDICAL SCIENCE

MEDICINE

UNDER THE CHARGE OF
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PERNICIOUS ANEMIA.

Etiology.—Although the stomach in pernicious anemia has held the interest and attention of many observers for over 50 years, especially since Henry and Osler¹ described in this journal the morbid changes present, it was not until 1929, when Castle² published, also in this journal, his important observations, that an understanding of the rôle of the stomach began to unfold itself. These studies and subsequent contributions by Castle and a legion of investigators stimulated by his work, have not only established the pathogenesis of pernicious anemia upon a solid foundation but have also brought to light an understanding of the etiology and therapy of certain related macrocytic anemias, and have aided greatly in the establishment of the rôle of the gastro-intestinal tract in some microcytic anemias. Such information has also led to a rational therapeutic classification of the anemias.

The classic description of the patient with pernicious anemia has long included many characteristics which may make diagnosis by inspection from the foot of the bed possible. The rather well nourished lemon-tinted individual with blue eyes, fair complexion and prematurely gray hair is familiar to all of us. And further, the rarity of the disease in dark-skinned peoples and tropical residents has added to the conviction that a certain diathesis may underlie the development of this disease. Pernicious anemia is rare in Egyptians. Orientals^{3,4} are peculiarly immune to its ravages. Negroes^{5,6} seldom develop the disease. Only once was it diagnosed in approximately 8500 negro admissions to a large metropolitan hospital. At the Charity Hospital in New Orleans, however, Jamison⁵ found its incidence somewhat higher. Many doubt its occurrence at all in the full-blooded negro.

These interesting phases of pernicious anemia have prompted Friedlander⁷ to analyze 500 cases from the standpoint of constitutional types. His results confirm the greater frequency of the disease in white races,

especially in temperate zones, and further tend to show that within this group the light complexioned, fair-haired individual is most often affected. Percentage occurrence in Nordics was high. Dark complexioned and heavily pigmented patients almost invariably gave a history of fair complexioned ancestors or siblings.

The evaluation of such a factor, especially since many patients do not fit the constitutional type, is so bound up with the complexities of heredity that until analyses reach a mathematical stage, one must be satisfied with generalizations.

Barron⁸ states that seldom do pernicious anemia and tuberculosis occur together. Those with pernicious anemia are practically free from tuberculosis, and on the rare occasions when the two diseases are associated, miliary tuberculosis is somewhat more common than other types. When associated in the same patient, each disease appears to run a course entirely uninfluenced by the other. To Barron the infrequent association of the two processes means antagonism. On the other hand, there appears to be an association between diabetes mellitus and pernicious anemia. Watson⁹ regards the relationship as more than coincidental. In 24 of 31 cases, Root¹⁰ noted the occurrence of diabetes before the onset of the anemia. Watson also noted this relationship. Possibly the effective therapy now in use in both diseases has increased the occurrence of the two simultaneously. Both, as well, have important hereditary aspects. Certain diabetics follow diets which could easily be inadequate in elements necessary for proper hematopoiesis, especially in the presence of altered gastric secretion often seen in diabetes.

The literature contains many data tending to demonstrate an inter-relationship between pernicious anemia and idiopathic hypochromic anemia.¹¹ Heath has described a family with what he believes to be an inherited tendency to reduced gastric function. Pernicious anemia and idiopathic hypochromic anemia were both present in 3 sisters, and other members of the family displayed borderline cases of both macrocytic and microcytic anemia. Reports¹² are on record of the transition of the microcytic anemia into a macrocytic type.

When Castle¹³ published his epoch-making observations demonstrating the presence in the gastric juice of normal individuals of an hitherto unknown substance, the intrinsic factor, which in the presence of certain foods, notably beef protein, an extrinsic factor, yielded a product which on absorption into the blood stream caused a remission in pernicious anemia, the way for an intelligent understanding of macrocytic anemia was cleared. The intrinsic factor was shown to be related to no known substance in normal gastric juice. Storage of this product, or one derived from it, appeared to occur in the liver. Thus, not only was it possible to correlate intelligently the efficacy of such preparations as hog stomach and liver in the treatment of pernicious anemia, but the relationship of many conditions producing the pernicious anemia blood picture could then be worked out.

Castle and his associates^{14,15,16} define pernicious anemia as a deficiency disease conditioned by the lack of a specific factor. They describe three reactions by which macrocytic anemia may be produced: 1, pernicious anemia due to a lack of the intrinsic factor; 2, sprue, and at times pernicious anemia, mainly due to a lack of the extrinsic factor;

and 3, pernicious anemia due to defective absorption or utilization of the product of interaction of the intrinsic and extrinsic factors.

One is easily confused by the diversity of opinion regarding the nature of the extrinsic factor. Not only does it occur in beef muscle, but it has also been demonstrated in many other foods such as liver and liver extract, rice polishings, autolyzed yeast and eggs. The statement by Castle in 1932 that the extrinsic factor was vitamin B₂ and a subsequent communication,¹⁴ that the reactions of the extrinsic factor correspond to those of vitamin B₂ have led to considerable investigation of the subject. Wills¹⁷ and Wills and Naish¹⁸ were unsuccessful in their attempts to confirm the views of Castle. Lassen and Lassen¹⁹ were also unsuccessful in demonstrating a relationship to the vitamin B complex and an editor's note in their paper quotes Castle as being prepared to relinquish his views. Miller and Rhoads,²⁰ however, feel that the small amounts of vitamin B used in Wills' observations make her work inconclusive. By incubating 100 gm. of egg white containing 20 rat units of vitamin B₂ with 150 cc. of normal human gastric juice, reponses were obtained. Similar results were obtained with rice polishings, a substance with a known high content of vitamin B.

With such conflicting evidence one can but conclude that the question is still an open one. Whether or not the extrinsic factor is the vitamin itself, it is found uniformly in foods rich in the vitamin B complex.

No more settled than the identity of the extrinsic factor is the nature of the intrinsic factor. It is thermolabile and according to Castle's theory, requires a substrate (the extrinsic factor), properties which are usually identified with enzymes.²¹ Contrariwise, the work of Morris²² has demonstrated its ability to withstand the chemical treatment known to destroy enzymes. It is dialyzable and exhaustible, observations which have led Morris to the hormonal concept ("addisin"). The work of Greenspon²¹ favors the latter view. The nature of the intrinsic factor remains, then, an unsolved problem of hematology and gastro-enterology.

Since the nature of both the intrinsic and extrinsic factors is unknown, it is not surprising that the nature of the product of their interaction, the hematopoietic factor, is also unknown. As with the building stones which allegedly produce it, attempts to purify, isolate and identify the principle have not met with success. Nevertheless, results of the investigation of its chemical nature have been most interesting. The work of Cohn is too well known to warrant further comment. Recently Kyer²³ and Subbarow, Jacobson and Fiske²⁴ have attempted to isolate the active principle by adsorption on charcoal, and later elution with alcohol. By chemical manipulation the latter group has fractionated the active principle so obtained. Three fractions were obtained, two crystallin in nature. Although each alone was inactive, mixtures were highly active clinically. The relationship of these fractions to the intrinsic and extrinsic factors is obscure.

In their most recent observations, Dakin and West,^{25,26} starting with commercial liver extract, have succeeded in obtaining a product 30 mg. of which causes a perceptible reticulocyte response and 80 mg. a maximum response in patients. The method of purification differs fundamentally from that of Subbarow, Jacobson and Fiske. Inactive material was removed by precipitation with alcoholic calcium acetate

followed by precipitation of the active material with Reinecke acid. Further purification was done by a salting out process. Chemical analysis of the product obtained by Dakin and West and that of Subbarrow, Jacobson and Fiske shows marked differences, for example, in nitrogen content, differences which are dependent, no doubt, upon the two methods of purification and upon the fact that neither product is a pure one.

The theory of Castle has not gone unchallenged. At least four groups have raised objections.^{21,22,27,28,29} The work of Castle swept into the discard the theory of toxins and toxic products as a cause of pernicious anemia. A renewal of interest in this theory appears to be arising with the reports of European observers³⁰ of success in production of remissions in pernicious anemia by the intravenous injection of Congo-red. The reported confirmation of these methods by Mermod and Dock²⁹ in this country led the latter observers, because of known neutralizing effects of Congo-red on toxic agents, to suggest a further exploration of the toxic theory. The demonstration by Wakerlin and Bruner³¹ of a toxic reticulocyte depressing factor in the urine of patients with pernicious anemia in relapse adds weight to the suggestion of Mermod and Dock. Macht and Gardner's³² demonstration of the phytotoxic action of pernicious anemia serum, persisting even in the stage of remission, lends further support to the toxic hypothesis.

While Mermod and Dock obtained reticulocyte responses in guinea pigs with Congo-red, therapy with this dye in clinical pernicious anemia was not carried to full remission. One must remember, too, that reticulocyte responses occur to many products given parenterally in the absence of the specific response as seen to liver in pernicious anemia. In recent reviews of the interpretation of reticulocyte responses by Minot³³ and Minot and Castle³⁴ emphasis is laid upon the fact that such responses to liver therapy in pernicious anemia "are orderly and simulate the curve for growth and death of organisms and their cells." Such characteristics are necessary to proper interpretation and one should be hesitant in interpreting reactions not conforming to these characteristics as specific.

As previously stated, Morris and his co-workers published evidence to show that a gastric hormone or enzyme, "addisin," acts as a stimulus to hematopoiesis in pernicious anemia without the necessity of an extrinsic factor. This substance is supposedly diminished or absent in pernicious anemia. Whereas Conner³⁵ reported confirmation of Morris' work, Fouts, Helmer and Zerfas³⁶ were unable to isolate addisin by ultrafiltration unless some change has taken place in the gastric juice. Storage in the ice box for 2 months followed by concentration by ultrafiltration produced an active product, as did fresh gastric juice concentrated by vacuum distillation.

Three possible explanations for the results are given: 1, There may be interaction of an intrinsic and an extrinsic factor. Although the extrinsic factor has not been demonstrated in human gastric juice protein substances could act in this way. The fact that signs of muscle destruction are absent at the site of injection and that fresh gastric juice concentrated by ultrafiltration is inactive is against an interaction occurring at the site of injection. 2, The possibility exists that reticulocytes may have been produced by toxic substances. The observations of Minot have already been cited that reticulocytosis

may result from parenteral products, such as Fowler's solution and non-specific proteins. According to Minot, such responses are usually prolonged and without orderly progression, not unlike those of Morris and Fouts, Helmer and Zerfas. Fouts recognizes the unusual character of the reticulocyte responses observed by him and his associates. 3, The third possibility is the activation of a gastric hormone. The data do not support this supposition.

Morris³⁷ also suggested that an excess of addisin, "hyperaddisinism," might explain erythremia and that gastric lavage is rational therapy for this condition. The evidence of Briggs and Oerting³⁸ and Kraemer and Asher³⁹ in carrying out this manipulation is not conclusive. Furthermore, it is very unlikely that the gastric principle does any more than add a factor which is necessary to permit maturation of the red blood cells. Oxygen tension of the bone marrow, not a gastric principle, appears to be the normal stimulus to red blood cell production. Were the gastric principle the stimulus, excess liver extract would necessarily produce polycythemia, a condition not seen in overdosage.

In the interpretation of Bloomfield and Pollard²⁸ the theories of Castle play a narrow and restricted rôle in hematopoiesis. These authors have followed a group of individuals with unexplained gastric anacidity for periods varying from 1 to 12 years. There was no suggestion of the development of pernicious anemia. Attempts to demonstrate Castle's factor in several cases of anacidity without anemia failed.⁴⁰ Quantities of hematopoietic factor found in the low-volume mucoid secretion of such patients hardly seemed sufficient to keep blood values normal. Says Bloomfield, "All this to our minds indicates that the absence of Castle's intrinsic factor in gastric juice does not necessarily lead to the development of pernicious anemia." Only an occasional person requires such protection. Rarely following gastric resection does macrocytic anemia develop. In carcinoma of the stomach the anemia is usually microcytic. Desiccated dog stomach⁴¹ is only one-half as effective as that of swine.

Greenspon²¹ adds a new interpretation to the results of Castle's experiments in his postulation of a theory quite similar to that of Morris. Greenspon believes that the hematopoietic response results from the activity of a gastric hormone without the necessity of an extrinsic factor. His experimental data show an hematopoietic response to gastric juice when peptic activity is destroyed or prevented by alkali or cold temperatures. Pepsin, he states, has a strong affinity for protein which adsorbs it from a fluid medium. Depcpsinized but otherwise normal gastric juice without an extrinsic factor was found to be effective in therapy. The beef in Castle's basic experiment supposedly adsorbs the pepsin which then cannot destroy the hematopoietic principle. The effectiveness of ventriculin is ascribed to the inactivation of pepsin by the muscularis. It is possible on the other hand, that the extrinsic factor under attack was not completely excluded under the condition (FitzHugh⁴²) of Greenspon's experiments.

Greenspon's theory, as yet not confirmed, appears from the data given to explain adequately anemias classified by Castle as due to a loss of the intrinsic factor. A consideration of the anemias due to a loss of extrinsic factor alone finds small place in the interpretations of Greenspon. In such cases his explanations are weak indeed. He suggests

the possibility that the substance containing the so-called extrinsic factor includes factors which stimulate cells of the stomach or furnish elements for synthesis.

If the intrinsic factor is absent in patients with pernicious anemia, why do any red blood cells mature at all? Why should various patients have in relapse varying red blood cell levels? Such questions have stimulated Goldhamer^{43,44,45} to a study of these aspects of the disease. Castle had noted¹⁵ a reappearance of the intrinsic factor in 1 patient following use of liver extract and suggested that the defective production of the intrinsic factor is relative and not absolute. Goldhamer's results support this statement. He collected gastric juice from 26 patients with pernicious anemia in relapse. Secretion averaged 20 cc. per hour as compared with 150 cc. for the normal. Repetition of Castle's experiment with this gastric juice in quantities comparable to those of the normal individual gave responses suggesting that patients with pernicious anemia do secrete the hematopoietic factor but in deficient quantity. A direct relationship was found between the volume of gastric juice and the red blood cell level in relapse. It is conceivable that a defective supply of extrinsic factor might, in a patient with a reduction of the intrinsic factor to a critical level, precipitate anemia. Such a mechanism may explain the response of some patients to autolyzed yeast,^{46,47} especially since these products are not effective parenterally.⁴⁸

To state simply that pernicious anemia is usually due to a loss or deficiency in the intrinsic factor seems simple enough. But why is it absent or deficient? The cause is apparent in gastrectomy, polyposis and carcinoma of the stomach. But the why of its absence in true pernicious anemia is seldom the topic of investigation. The work of Miller and Rhoads in demonstrating the disappearance of the intrinsic factor from the stomachs of experimental animals on vitamin B deficient diets appears to concern itself more with the pathogenesis of sprue and pellagra than with pernicious anemia. The possibility of a constitutional factor has already been discussed. The work of Bloomfield and his associates correlates well with this view. The reduced volume of secretion with achylia gastrica is probably very important in the light of Goldhamer's observations. That the principle may or may not occur in achylia⁴⁹ indicates that it alone is an insufficient explanation. The absence of the intrinsic factor in the presence of free hydrochloric acid⁵⁰ demonstrates the lack of dependence upon the acid factor.

The extensive observations of Castle and his associates upon patients with sprue⁵⁰ demonstrate its intimate relationship to pernicious anemia. The same systems (nervous, gastro-intestinal, hematopoietic) are involved in both diseases. Castle states that at times, "It was beyond our clinical ability to decide whether the condition under observation in Puerto Rico was sprue or pernicious anemia." Patients demonstrated an interference with one of all three mechanisms possible in the development of macrocytic anemia. Sometimes the extrinsic, sometimes the intrinsic factor was lacking while in other cases absorption from the intestines was the important defect. Recently Miller and Rhoads⁵¹ have demonstrated roentgenographic changes in the small intestine in patients with sprue. A return toward normal form and function

followed the injection of liver extract, suggesting that liver extract parenterally conditions the functional activity of the small intestine.

Pellagra, as well as sprue and pernicious anemia, involves the gastrointestinal, nervous and hematopoietic systems. The work of Miller and Rhoads⁵² on the effect of vitamin B₂ deficient diets upon swine may be recalled here. Stomatitis, gastric anacidity and a macrocytic anemia amenable to liver therapy, resulted. Spies and Payne⁴⁹ have shown the presence of the intrinsic factor in the stomach of pellagrins with achylia gastrica. The association of vitamin B₂ with the extrinsic factor and its place as the alleged cause of pellagra gave promise in associating the two diseases. The work of Spies and Payne,⁵³ however, speaks against such an association. In demonstrating that pellagrins improve on yeast, which when incubated with normal gastric juice, caused no remissions in patients with pernicious anemia, they suggest that the chemical substance in yeast utilized by the pellagrin to remit his disease is not the same as the precursor of the anti-anemic factor in food.

A fourth mechanism for the development of macrocytic anemia appears evident in the association of cirrhosis of the liver with macrocytic anemia. While such an association has been known for years, it remained for Wintrobe and Shumaker⁵⁴ and Van Duyn⁵⁵ to re-awaken interest in the subject. The occurrence of free hydrochloric acid in the gastric contents of these patients speaks against a mere association of cirrhosis and pernicious anemia. Such patients, then, are capable of producing and adsorbing the hematopoietic factor; but, because of liver disease, they are either unable to store or further elaborate upon the principle. Goldhamer, Isaacs and Sturgis¹⁰⁵ suggest that the liver may be sufficiently damaged so that the principle, although present, cannot be presented to the tissue for utilization. Its absence has been demonstrated in the cirrhotic liver.

Van Duyn⁵⁵ has suggested that the patients with macrocytic anemia and free hydrochloric acid should be suspected of liver disease. He regards this combination of findings as a sign of hepatic dysfunction. Such findings could be present as well in the macrocytic anemia of gastric syphilis or polyposis, intestinal stenosis and sprue.

A number of negative findings of interest have been reported recently. Stare and Thompson⁵⁶ can attach no significance to the flavins in pernicious anemia. Alt⁵⁷ finds only hypochromic anemia in experimental goats' milk anemia. Previous reports have described this anemia as hyperchromic. Watson,⁵⁸ having in mind the demonstration by Hans Fischer of increased coproporphyrin in the urine of patients with pernicious anemia in relapse, isolated this substance from the feces of similar patients. While coproporphyrin has been identified in Germany with the erythroblasts and megaloblasts of pernicious anemia marrow, its significance remains unknown. The fact that it occurs in brewers' yeast, and is increased by autolysis suggests a possible relationship to the extrinsic factor. The American literature shows no investigation of this aspect of porphyrin metabolism. Helmer, Fouts and Zervas^{59,60} found no correlation between the pancreatic enzymes and the maintenance dose of liver extract. Goldhamer⁶¹ has found that the retarded rate of glycolysis in pernicious anemia is proportional to the red blood cells decrease. He finds that an increase in

the rate of glycolysis per hour per million red blood cells in early remission is associated with an increase in reticulocytes.

Pathology. Postmortem observations, such as those of Brown,⁶² have demonstrated a great variety of morbid changes in the gastrointestinal tract of patients with pernicious anemia. In Brown's series of 151 cases, 60 showed evidence of old intraabdominal infection, and, in all cases but 1, microscopic evidence of chronic inflammation was found. Chronic gastritis occurred in 41 of 42 specimens studied microscopically. Adhesions and partial intestinal obstruction were frequent findings.

Although achylia gastrica has long been described as an invariable accompaniment of Addisonian pernicious anemia, note has already been made of occasional exceptions to this rule. Most studies of the gastric state in pernicious anemia have been carried out postmortem. Recent observations by Jones, Benedict and Hampton⁶³ in living patients by gastroscopic, roentgenologic and direct observation at operation demonstrate that, contrary to generally accepted views, atrophy of the stomach is not an invariable accompaniment of pernicious anemia. Under adequate liver therapy over a period of months, all evidences of atrophy disappeared in 2 cases with a return to a normal appearance. Tissue sections at operation were confirmatory. An hypertrophied stomach was noted in 1 case and all showed evidence of chronic inflammation.

Heck and Watkins⁶⁴ describe a "shift to the right" in the neutrophil of pernicious anemia. Exceptions were encountered, however, in which a shift to the left was found. No relationship of hypersegmentation to the degree of anemia was observed. Finer structural changes in the nuclear skein were also noted.

Symptomatology. Greatest interest in the symptomatology of pernicious anemia lies at the present time in the field of neurology. Such rare associations as the Parkinsonian syndrome with pernicious anemia deserve little comment. Brain tumor may be simulated even to the occurrence of papilledema.^{65,66}

There is great diversity in the statistics recorded by various authors as to the frequency of spinal cord and cerebral symptoms. For example, cerebral symptoms are reported in from 4 to 64% of patients.^{67,68} Such great variations mean, no doubt, differences in criteria for their recognition. Most symptoms of cerebral origin are those usually found and included in the term toxic psychosis. Hallucinations, apathy, delusions, stupor and symptoms resembling the more important organic psychoses are present. Diversity of opinion lies not only in the expression of such symptoms but also in their relationship to the pernicious anemia. Tenny and Goldstein⁶⁸ are of the opinion that familial and personal predispositions are important factors in their production. Osgood,⁶⁹ as well, concludes from 17 cases analyzed that the association of psychoses with pernicious anemia is probably largely incidental. On the other hand, Parfitt⁷⁰ and Pren and Geiger⁷¹ believe that, through toxemia or actual organic lesions, pernicious anemia is directly responsible for the psychotic manifestations. The latter observers attribute the differences in interpretation and incidence of the symptomatic psychoses to the failure of the internist to apply the established criteria

of psychiatry to these patients and a similar failure on the part of the psychiatrist to recognize the accompanying anemia.

The incidence of cord changes is reported much higher than the incidence of cerebral changes. Goldhamer, Bethell, Isaacs and Sturgis⁶⁷ found 364 out of 408 cases with neurologic changes. Of these, posterior column involvement occurred in 89.2%, lateral column involvement in 41.6%, and combined disease in 40.7%.

Diagnosis. The group of seemingly unrelated clinical states producing the pernicious anemia blood picture, for example pernicious anemia, sprue, celiac disease, multiple intestinal anastomoses and fish tape-worm infestation, although all having in common one factor, the involvement of some portion of the gastro-intestinal tract, defied adequate explanation of their relationship to each other until the work of Castle in 1929. Since then, as has been mentioned under Etiology, a classification of the macrocytic anemias according to mechanisimal disturbance has been possible. Disturbances in pernicious anemia, sprue, pellagra and cirrhosis of the liver have already been mentioned. In the macrocytic anemias of gastric syphilis and carcinoma, polyposis of the stomach and gastrectomy, the pathogenesis is evident. In intestinal adhesions, anastomoses and stenoses and in the diarrhea of celiac disease, a disturbance in absorption suggests itself. All patients showing the pernicious anemia blood picture deserve study for the presence of one of these detectable disturbances, cure of which may lead to permanent remission of the anemia. This is especially true in the presence of free HCl in the stomach, as suggested by Van Duyn.⁵⁵ Although Van Duyn regards the presence of macrocytic anemia and free HCl in the stomach as a sign of liver dysfunction, it may be used as a sign indicative of macrocytic anemia associated with gross gastric disease or extragastric disease which may be capable of correction.

The diagnostic approach of Beebe and Wintrobe⁷² to doubtful and obscure cases of pernicious anemia is worthy of repetition. The gastric juice of the suspected case, when incubated with ground beef, is compared in its effects with that of known individuals when fed to known cases of pernicious anemia in relapse. The test is described as of diagnostic assistance 1, when arteriosclerosis, infection and chronic disease make the response to therapy inadequate; 2, in cases of damage to the spinal cord with little or no anemia when the blood does not make the diagnosis and 3, in patients with little anemia, receiving liver, and in whom, if treatment were stopped for diagnosis, nervous symptoms might develop.

Treatment. Most patients with pernicious anemia may be treated adequately by the ingestion of liver. However, monotony of diet and distaste for liver, together with scientific inquisitiveness, have led to the development of many concentrated preparations of liver extract available commercially. Since therapeutic effect is dependent upon proper standardization of dosage the method of assay becomes most important. In the absence of the purified principle, assay depends entirely upon biological effects, and in this instance upon the reticulo-eyte response.

Attempts have been made to free the assay of liver products from dependence upon patients in relapse. Laboratory animals, especially guinea pigs and pigeons, have been used for this purpose. Jacobson^{73,74}

in controlling the variables of diet and environment in the guinea pig, and with the use of control periods, reports the demonstration in picked animals of reticulocyte responses, a quantitative expression of hematopoietic activity being recorded as guinea pig units. Such assays conform with expected results⁷⁵ with the liver of patients with pernicious anemia in relapse and in remission, as well as with the liver of non-anemic patients.

On the one hand, the work of Jacobson has been confirmed,⁷⁶ on the other hand, Goodman, Geiger and Klumpp⁷⁷ report responses similar to those of Jacobson after normal saline alone. They interpret all their reactions as spontaneous or non-specific.

Attempts to use as test animals pigeons on an inadequate diet to decrease the percentage of circulating reticulocytes have given results⁷⁸ indicating wide fluctuations in percentage of reticulocytes without significant effects by the test substances. Such observations indicate clearly that for accurate therapeutic assay, we must still rely upon the patient in relapse.

Minot's interpretations of reticulocyte responses have already been noted. He states further that the character of the reticulocyte response varies with: 1, the initial red blood cell level; 2, the amount of active material given; 3, the portal of entry; 4, the rate at which the materials enter the body and, 5, the reactive state of the bone marrow. The initial red blood cell level is most important in biological assay. Reticulocyte responses expected with full dosage of active potent material have been worked out for the various initial red blood cells levels below three million. Bethell⁷⁹ and Bethell and Goldhamer⁸⁰ have shown that the reticulocytes bear an inverse relation to the number of red blood cells. Mathematical expressions of these relationships have been formulated for both oral and parenteral administration. Recent establishment of such criteria for potency of liver preparations by the Council on Pharmacy and Chemistry of the American Medical Association⁸¹ places the commercial preparations so approved upon standards which assure the physician of the potency of the material used.

There have been three well known methods used to increase the potency of liver. Methods of concentration such as that of Cohn, of Subbarow, Jacobson and Fiske, and of Dakin and West have already been considered. Increased potency has also been claimed by liver autolysis. By this method Herron and McEllroy⁸² claim to have produced a preparation with an oral dose approaching that of the parenteral route. A commercial preparation was offered to the profession upon the basis of this work. Castle and Strauss,⁸³ however, found that with both experimental and commercial autolysates less hematopoietic activity resulted than with comparable amounts of liver from which they were derived. Their analysis of Herron and McEllroy's cases does not support the reported conclusions. Klumpp's results⁸³ are in complete agreement with those of Castle and Strauss. He found, however, that the autolyzed liver is effective in the initial and maintenance treatment of pernicious anemia and that the autolyzed liver concentrate was more potent than a commercial extract derived from the same amounts of liver. Conner and McQuiston,⁸⁵ from their results with autolyzed liver, state that "It seems justifiable to say that the preparation which we used in clinical trial (commercial preparation) is not

reliable in the dose recommended and in some cases it is not reliable in even double this dose. It seems that it cannot be said definitely that autolysis either increases or decreases the effectiveness of liver in the treatment of pernicious anemia."

The third method in use for increasing the potency of liver preparations is digestion with normal gastric juice. First carried out in Europe with whole liver, the procedure has been repeated in this country both with whole liver and liver extracts. Although Barnett and Thebaut⁸⁶ were unable to obtain positive results the subsequent work of Walden and Clowes⁸⁷ and Fouts, Helmer and Zeifas⁸⁸⁻⁹¹ demonstrates conclusively a marked increase in potency of extracts so treated. Assays were carried out upon clinical cases of pernicious anemia. Maximal reticuloocyte responses were produced only when definite amounts of gastric juice and liver extract were used. Fouts and his associates believe that the increase in potency is a result of the type exemplified by the interaction of beef muscle and gastric juice rather than an actual increase in the active principle originally present in liver.

The production of active preparations suitable for parenteral use has led to a widespread adoption of this form of therapy. McHenry, Mills and Farquharson,⁹² although finding the potency of intramuscular extracts approximately thirty times that of oral products, find no better results than with adequate oral therapy. Parenteral therapy is distinctly advantageous in those patients in severe relapse or those refractory to oral therapy.

There are distinct advantages to intramuscular therapy. Murphy⁹³ enumerates the advantages as 1, certainty of dosage under absolute control; 2, rapid response in severe relapse; 3, response of "resistant cases;" 4, efficacy of treatment in combined system disease; 5, convenience of infrequent injections in uncomplicated cases; 6, economy in the cost of material; 7, the freedom of the patient to travel. He⁹⁴ has found it possible to maintain patients upon extracts from 100 gm. of liver with injections at 1 to 6-week intervals. Sherman⁹⁵ has spaced doses at weekly intervals but was unable to determine the exact dosage before treatment. Others as well⁹⁶⁻⁹⁹ have been able to space injections as infrequently as 1 month apart in some cases. Individual variations in patients, however, are most important in the determination of the proper amount and the spacing of medication. Intravenous products^{98,99} have been successful in preliminary studies but as yet are undesirable for routine treatment.

The method of Haden¹⁰⁰ for the determination of adequacy of treatment is both simple and satisfactory. Since glossitis and parasthesias may disappear and the blood values may be above the accepted lower limits of normal, yet submaximal for the individual under consideration, the red blood cell count alone is unsatisfactory. Haden believes that macrocytosis supplies a sensitive indicator of adequacy of treatment. "This is the first hematologic manifestation of the disease and persists when all other signs are gone, so is by far the most valuable indicator of the deficiency." Absence of macrocytosis, then, indicates complete remission.

The greatest controversy in the treatment of pernicious anemia lies not in the hematologic response but in the response of neurologic changes. Reports are most conflicting, due in part according to Garvey,

Levin and Guller¹⁰¹ to the variations in criteria used. Subjective findings often improve with therapy. These, too, may be difficult to evaluate in a patient with cerebral symptoms. Also, subjective findings are inherently difficult to classify.⁹⁸ Spontaneous variations in the absence of treatment may add further confusion to interpretation. There are those^{68,97} who believe that liver therapy may not only arrest the progress of nervous manifestations but may actually cause objective signs to disappear. Most authors^{67,98,101,102,103} are less optimistic. Farquharson¹⁰³ reports complete arrest of the progress of the neurologic manifestations in all patients taking the prescribed amount of liver and improvement in neurologic symptoms especially if of short duration. Best results were obtained with intramuscular liver. Adequate dosage is described as the amount required completely to arrest progress of the lesion. Since such doses cannot be predicted, Farquharson suggests the use of two to three times the dose commonly used without cord lesions. Mills' results have been somewhat similar.

Fouts and Zerfas have observed patients in whom large amounts of liver extract were insufficient to prevent progress of nervous involvement. Grinker and Kaudel believe that liver is not effective in preventing cord degenerations. Goldhamer, Bethell, Isaacs and Sturgis found improvement in symptoms in less than 50% of the cases and in signs in about 2% with adequate anti-anemic therapy. They believe that anti-anemic therapy does not have a specific curative effect upon spinal cord degeneration but contributes only indirectly to such improvement. The course of the disease in individual cases varied widely.

Strauss, Solomon, Schneider and Patch¹⁰⁴ list as reasons for failure of results to agree: 1, evidence of the effectiveness of treatment must be judged by the evidence of arrest of the process and not by the degree of improvement, for regeneration of destroyed spinal nerve cells cannot be expected any more in pernicious anemia than in tabes dorsalis; 2, the improvement in the neurologic state may be entirely due to improved general health, reeducation and similar factors. Peripheral nerve changes may completely disappear; 3, cord lesions do badly in the presence of sepsis; 4, short observations may lead to abandonment of hope of improvement before adequate therapy is given. Their results indicated: 1, in no instance did an objective sign progress nor a new one appear; 2, subjective improvement occurred in all patients; 3, except for gait and paresthesias, about 58% of all abnormal signs were objectively unchanged.

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PEDIATRICS

UNDER THE CHARGE OF
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MACON, GEORGIA.

PREMATURITY AND IMMATURITY AS MEDICAL PROBLEMS.

According to Hess¹ a mature baby is one born at term, or at the end of from 270 to 290 days of gestation, irrespective of the degree of development of the baby. Classified as immature is any infant, whether

a single or multiple birth, born prematurely, at term or even past term, whose weight is below 2500 gm. ($5\frac{1}{2}$ pounds). Such infants are not completely prepared for full, normal, independent extrauterine existence. Premature infants comprise a large number of those classified as immature. A consideration of premature infants would not cover all of the problems of the undersized baby as there are many born in single birth beyond the average normal period of gestation which, because of their weight and size, must be considered in this category. There are also the majority of infants of multiple births who qualify for this classification.

The problem of the undersized and underdeveloped infant has received much consideration from the medical profession. Methods and apparatus for the care of these have been well established for many years. As a result, innumerable cases have been reared successfully by the physicians of this and other countries. Although the presence of a problem of this sort would hold the interest of the family and closer circle of friends, as a rule, the general public has been unaware of these cases except in unusual instances. The reward of the host of doctors, who have participated in the direction of the care of these babies, has been found in their own satisfaction in the results. The multiple delivery resulting in the birth of the 5 female babies, now famous as the Dionne quintuplets, has centered the interest of the world in their problem, and has aroused professional and lay interest in the protection and care of the subnormal baby. Through the interest manifested and by means of the funds secured from various sources, it has been possible to crystallize around these sisters all of the worthwhile developments of previous decades.

Early in the consideration of this subject the question arises as to the frequency with which immature and premature babies are seen. Inquiry was made to several national and federal agencies. From the lack of reply on this point it is presumed that such figures are not available. The certificates of birth in use do not require information on this point. The only statistical data available are the mortality figures for premature infants, as arranged by Dunn² as follows:

Death and death rate per 100,000 estimated population from premature birth in United States, 1930-1934.

Year.	Deaths.	Rate.
1934	35,102	*
1933	32,953	26.2
1932	33,143	27.6
1931	34,477	28.9
1930	37,433	31.6

* Not available.

Dr. E. C. Tandy³ summarized these figures as follows: "The number of deaths under 1 year from premature birth in the United States in 1933 was 32,953, and in 1934, 35,102. The majority of these deaths occur in the first month of life. In 1933, 31,796 occurred during that age period." From a table furnished by her, based upon Bureau of Census figures, are noted on page 142.

Year.	Death under 1 month.	Rate per 1000 live births.
1921	27,932	16.8
1922	26,835	17.0
1923	26,816	16.7
1924	27,409	16.7
1925	26,075	16.4
1926	26,334	17.0
1927	25,300	16.2
1928	25,273	16.7
1929	24,149	16.5
1930	23,204	15.7
1931	21,426	15.3
1932	20,629	15.1
1933	19,718	15.3

These figures show a tendency toward a decrease in the total number of deaths of premature babies during the first month of life. The mortality rate of such deaths per 1000 living births has fallen in a period of 12 years from the highest rate of 17 to 15.1. When the number of deaths during the first month of life is compared with the total number of deaths of premature babies for the years that such figures are available, it is seen that the great preponderance of such deaths occur in the first month. Premature and immature babies that can be carried beyond this age have far better and increasing chances of surviving. Although there has been a decided decrease in the mortality rate for this age period of premature babies as shown in the above table, the toll is excessively high.

On the basis of the generally accepted classification of prematurity on a weight of less than 2500 gm., Milio⁴ studied 1000 deliveries. The majority of the infants were born between the 270th and the 290th day of pregnancy. The majority of the infants born during the usual physiologic limits of pregnancy weighed from 3000 to 3500 gm. and were considered as normal. A considerable number weighed less than 2500 gm. and were imperfectly developed organically and functionally, or immature. In such babies the intrauterine life, although it may have been within the normal limits, had not been sufficiently long for these infants to mature. On the other hand, some of the babies in pregnancies shorter than 270 days were of the normal birth weight and apparently mature. Therefore, there must be some other elements besides the length of gestation which determine whether or not the baby is to be normal in size and development. About 12.9% of the 1000 cases studied by Milio weighed less than 2500 gm. This included only those born alive. He found that the following were the causes of the immaturity: "In 21 per cent, renal disease of the mother; in 16.2 per cent, multiple birth; in 15 per cent, diseases and anomalies of the organs of parturition and of the sexual organs, and in 11.6 per cent syphilis of the mother." Other causes were acute infectious diseases, diseases of the heart, tuberculosis and anemia of the mother. He could find no explanation in 21% of the cases of his series.

Hilgenberg⁵ observed in his clinic, between 1925 and 1930, 4368 deliveries. There were 214 living children weighing less than 2500 gm. This was an incidence of prematurity of 20.4%. Of these, 20% died before the age of 10 days. According to Clifford,⁶ the premature group

represents about 3% of the total births, but contributes one-half of the total neonatal deaths. Over 80% of the premature fatalities occur during the first 48 hours after delivery and pediatric care is without avail in preventing these deaths. He urged that this mortality can be reduced by delaying induction of premature labor whenever possible until a viable baby can be assured. His method is to make an estimation of the weight of the fetus *in utero* through mensuration of the occipitofrontal diameter of the fetal head by means of a modified roentgenometric technique. From this diameter the expected body weight can be judged. In the severer grades of toxemia the situation may arise wherein it is safer for the fetus to take its chance of being delivered as a premature infant than to run the risk of being stillborn if the pregnancy should be allowed to continue. The risk to the fetus in prematurity can be determined from information as to its expected birth weight. The expectation of premature death is in direct proportion to the difference between its weight and the average normal weight of a full-term baby. The smaller the baby the more likely is it to die. The old idea that 7-month babies are more apt to survive than those born at 8 months, is not borne out in fact. It is necessary, therefore, to consider the estimated weight of the baby against the severity of the toxemia in order to come to a decision. In pregnancy complicated by heart disease without failure of compensation, there seems to be little danger of intrauterine death of the fetus and pregnancy should be allowed to continue as far as the maternal condition will permit, but it is important to the future of the fetus that delivery should not be delayed until congestive failure develops, for this is another cause of high infant mortality. According to this author, the influence of knowledge as to the weight of the fetus *in utero* in the management of certain types of pregnancy has contributed to the reduction of the stillbirth rate to 47 in 1933 from a level of 69 per 1000 deliveries for the preceding 10 years. It has been instrumental in increasing the incidence of premature babies born alive from an average of 27.6 for the preceding 10 years to 34.7 per 1000 deliveries for 1933. The proportion of premature babies weighing from 4 to 5 pounds at birth increased from an average of 52% for the preceding years to 61% during 1933. The premature infant mortality dropped for the first time in 5 years from 35 to 29%.

Litchfield⁷ endorsed the opinion that syphilis is in large measure a primary factor in causing premature expulsion of the fetus. In his clinic there were found 56 stillbirths of which 40 had positive Wassermann records. Of these 40, 6 had a 4+ cord Wassermann. Autopsies on 21 other stillborn babies showed definite syphilitic lesions in 9.

Among other conditions during delivery requiring consideration, atelectasis is important. McGrath and Kuder⁸ performed resuscitation on 21 premature babies delivered by them; 13 died; 11 were examined postmortem and all showed atelectasis except 1. Another frequent cause of neonatal death of the premature is intracranial hemorrhage resulting from trauma during birth. Hilgenberg (*loc. cit.*) pointed out that in the underdeveloped infant the vascular walls tear very easily and cause congestion of the blood when subjected to force owing to the deficient development of the elastic fibers. Premature children also suffer more often from intracranial hemorrhage because of their

small size and the compressibility of their skull. The diagnosis of intracranial hemorrhage in the premature is extremely difficult for the reason that almost every premature baby presents the same picture as that of an infant with intracranial hemorrhage. Bonar⁹ stated that the diagnosis of intracranial hemorrhage of the newborn is based upon the symptoms of increased intracranial pressure. Minor hemorrhages are the most difficult to detect. Somnolence is the rule, although some infants are hyperirritable. In these the distressed or cephalic cry may be heard during sleep. Other signs are nystagmus, transient palsies of the eye muscles and minor cyanotic attacks. The two most important, but often unrecognized symptoms, are continued intermittent protrusion of the tongue (Foot's sign), and refusal to nurse. In the severe forms cyanotic attacks are more common, and there may be twitching of the facial muscles, increased muscle tone, rigidity, choreiform motions or athetosis, and even convulsions, as well as bulging of the anterior fontanelle.

The viability of premature infants is a mooted point. It is difficult to correlate for consideration in any particular case all of the factors for and against survival in the inheritance, in the infant itself and in the environment. However, there appear in the literature from time to time reports of the survival of very young and very small individuals. Fischer-Ban¹⁰ recorded the survival of an infant of 6½ months' gestation, weighing 600 gm. According to her, the previous low weight record with survival was 680 gm. This child received teaspoonful doses of tea for the first 12 hours, and after that a teaspoonful of breast milk every 2 hours. After the 8th day it was fed breast milk from a bottle and it was able to suckle at 3 months.

The question of the anemias of prematurity has engaged the attention of a number of observers. Josephs¹¹ studied a group of premature babies during the first 3 or 4 months of life. He attempted to determine the mechanism of the so-called physiologic anemia of prematurity. From his study of the reticulocytes he concluded that there is no basis for the idea that the fall in the red cells and hemoglobin was depended on hypoplasia in any strict anatomic sense. There was a period of failure to react to the administration of iron that lasted from 6 to 10 weeks after birth, the duration of the period depending on the degree of prematurity. After this early period of non-reactivity there follows a short transitional period, after which administration of iron was followed by a prompt response of reticulocytes with a rise in red cells and hemoglobin. There was no reason to believe that lack of stores of iron played any part in the development or persistence of the anemia before the end of the third month. Thereafter the rise in red cells without a corresponding rise in hemoglobin in untreated infants indicated the possibility that lack of stores of iron had become an important factor. From the results reported in his paper it cannot be concluded that a low percentage of hemoglobin is in itself harmful, although probably it is indicative of a condition that renders the infant more likely to succumb to infection. In such cases, although iron may raise the hemoglobin content, transfusion must still remain the method of choice in treating the condition as a whole. The evidence from this study does not permit of the conclusion that liver is necessary as an adjunct of iron, though in individual cases it may prove of benefit.

The same of the problem of the premature has been the subject of contributions by Merritt and Davidson¹² and Abt.¹³

According to Lowenburg,¹⁴ although the general principles necessary in the care of premature babies are well established and widely recognized, the application of these without individual discrimination will not be successful. A procedure applied successfully in 1 case may fail when applied in the next. This attitude of versatility toward the variations of the problems that appear from day to day or even sometimes from hour to hour is a prerequisite of success, especially in the very small baby. Among his recommendations are finesse of judgment, fine adjustment from day to day, and even the withdrawal or alteration of an order, if the reactions do not indicate that it is of benefit to the baby. In addition he emphasized intelligence and patience and the coöperation of a wise, calm and intelligent attendant.

Jewesbury¹⁵ pointed out the distinguishing characteristics of the premature child. The undeveloped state of the nervous system not only makes it more sensitive to external influences but also causes an inability to regulate and to maintain body heat. The relative surface area of the body is larger than in the normal baby and there is also an absence of subcutaneous fat. The suckling and swallowing reflexes are feeble or absent and, therefore, the nutritional intake is low. The underdeveloped state of the digestive system makes it more difficult for the premature baby to deal with any food except mother's milk. If this is rich, it may be necessary to modify the concentration of this to meet the capabilities of the premature stomach. There is a general low state of vitality with a consequent lack of resistance to infection. The heart, the lungs or other organs may be defective or too underdeveloped to function properly. This is the exception rather than the rule. In managing the premature baby prenatal conditions must be continued as far as possible. The essentials are warmth, sufficient fluid and food of a suitable kind and protection from infection.

Infection is an important element in infant mortality without regard to maturity or prematurity. Obviously the latter increases the hazards. Grulee, Sanford and Herron¹⁶ studied 20,061 infants from birth to 9 months of age. Of these, 48.5% were totally breast-fed, 43% partially breast-fed, and 8.5% artificially fed. The total morbidity of the breast-fed group was 37.4%, of the partially breast-fed group 53.8%, and of the artificially fed group 63.6%. The average mortality of these infants was 1.1%. Of this mortality, 6.7% were in the breast-fed group, 27.2% in the partially breast-fed group, and 66.1% in the artificially fed group.

Although the principles of the care of the premature baby are classical, it may not be amiss to review these with Jewesbury (*loc. cit.*). Special care must be taken from the moment of birth. The baby should be placed at once in a properly warmed receptacle. In order to minimize handling, it is recommended that the baby should not be oiled before 6 hours after birth, but the cord must be attended to in the regular manner. If the baby is very feeble, it should not be weighed. All the details of nursing, care and handling are exceedingly important, the main object being to conserve the baby's warmth and energy. At the outset the skin should be cleaned with olive oil every second or third day, until there is a steady gain in weight, after which the infant

should be oiled every day. When a weight of about 5 pounds has been attained, and then only if the baby is vigorous, a bath may be begun at first only every other day. The room temperature must be maintained at from 70° to 75° F., and when the baby is to be handled it is advisable to have even higher temperatures. In the maintenance of heat the cradle or basket is an important factor. Formerly incubators were used, but these have been found not to be essential. An electrically heated bassinet or a basket or cradle heated by some other means may be used. The source of heat and the method of securing this is not so important as is the necessity of regulating it to meet the varying needs of the infant. This is best judged by means of the temperature of the baby taken rectally. The clothing is an additional factor in the maintenance of the body heat. There are individual preferences as regards the clothing but Jewesbury's recommendations conform to the usual standards. He uses a binder of crepe bandage until the cord is off. A jacket is made by dividing Gamgee tissue and covering one side with gauze. This can be washed from time to time and is held in place better than the loose strips of wool or cotton that are sometimes used. A suitable petticoat and a woolly coat or sweater is used. The head should be covered with wool or a small woolen cap or bonnet. The feet and legs should always be kept warm and for this knitted woolen booties that come well above the knees should be used. The napkin should be soft and not bulky and need not be fastened until the child begins to be active. During the early phase it may be preferable to use a triangle of sterile cotton batting. Over all of the clothing a soft woolly shawl or light blanket should be added, so arranged that a corner can be used to cover the head of the baby.

In addition to the maintenance of body temperature the problem of fluid and food is the earliest need. The daily requirement of fluid is from one-sixth to one-fifth of the body weight. The amount of food and the frequency of feeding depend on the age, size and digestive capacity of the individual baby. Sometimes it is necessary to give the fluid at 2 or 2½-hour intervals, and in rare cases more frequently, but the 3-hour interval is usually satisfactory. The longer intervals should be aimed at in order to give the stomach time to empty and in order to allow the child more rest. Breast milk is usually preferable. This may be obtained from the mother or from other sources, and its concentration modified as condition requires. Usually it is necessary to feed this indirectly by means of a pipet, Breck feeder or bottle, but as the child grows and gains in vigor it may be suckled.

Hess¹⁷ also stressed that each premature baby is an individual feeding problem. He emphasized that vomiting and cyanosis are contraindications against increase in feedings. He stated that we must have a definite idea of the minimum food requirements for life. The amount of food necessary to maintain at least a stationary weight must be given, and in addition enough food to meet the requirements for growth and development. As soon as possible the feedings must be increased to from 90 to 100 calories per kg. of body weight per day and from one-sixth to one-fifth of the body weight in fluids as represented in the food and additional water. Under average circumstances this should be possible by the 10th to the 20th day. He recommended that from 140 to 180 cc. of breast milk per kg. of body weight daily should be

given. In Hess' Clinic skimmed lactic acid milk is added to the feedings of many infants. Such additions are started on the 4th or 5th day.

Lowenburg (*loc. cit.*) placed the daily caloric needs of premature babies at a minimum of 50 calories per pound daily and most of them at from 70 to 100 calories. He gave the fluid requirements as $2\frac{1}{2}$ ounces per pound of body weight per day. This amount should include the fluid given as such as well as that representing the feedings. Although he recommended the feeding of human milk, this author has found that evaporated milk is of great value in the care of the premature baby. He stated: "It truly represents *multum in parvo* in a digestible form: Prematures as well as other newborn babies have no difficulty in digesting evaporated milk, either diluted with water, with 5% glucose or with the hydrating solution of Kugelmass. It may be thoroughly digested, diluted or even entirely undiluted. Both cow's milk and human milk provide about 20 calories to the ounce, but evaporated milk represents 40 calories. Because of this additional food value one-half as much may be used in balancing the caloric needs of the baby. All sorts of combinations may be devised where individualization is most needed. In the babies that suckle well, have a fair stomach capacity and do not regurgitate, the problem of feeding is comparatively simple. Lowenburg rated tube feeding as of great value, but recommended feeding with a dropper or Breek feeder as preferable. In cases where tube feeding must be resorted to, he urged the avoidance of the nasal route because of the great danger of otitis media.

The problem of the reduction of the infant mortality rate in the United States is based very largely on the reduction of the premature births as nearly one-half of the deaths of the first year of life occur in the first month and nearly one-half of these are the result of premature birth. Our means and methods of caring for the underdeveloped baby are excellent, but the best results follow the individualization of the cases rather than the inflexible adherence to the set principles. The mortality rate may be greatly lowered by decreasing the incidence of premature births. Prenatal care of the mother is the main factor in accomplishing this. Careful handling and treatment of syphilis, tuberculosis, cardiac and renal disease, anemia and other diseases must be the rule. Another point to be emphasized is the avoidance of induction of labor until as late as possible in those cases where surgical intervention is necessary.

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PHYSIOLOGY

PROCEEDINGS OF

THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA

SESSION OF MAY 18, 1936

An Instrument for Uniformly Applying Painful Stimuli of Varying Intensity (Demonstration).—MICHAEL KNIAZUK (Merck Institute of Therapeutic Research, Rahway, New Jersey). One leg of a medium-sized forceps is broken by inserting a hinge and held in position by a tensed spring. In pinching, the force exerted between the tips of the forceps depends only upon the tension of the spring, which is adjustable. After the preselected tension, which may range between 150 and 450 gm., has been reached the spring is automatically released. The compression, and thus the intensity of the stimulus, is independent of the thickness of the object between the jaws of the forceps.

Improvements in the Testing of Analgesics and Local Anesthetics (Demonstration).—HANS MOLITOR, ALBERT LATVEN, and HARRY ROBINSON (Merck Institute of Therapeutic Research, Rahway, New Jersey). *Testing of Analgesics.* The method is based on the application of graduated pressure on mice's tails and statistical evaluation of the results. Through the use of a large number of animals of the same strain for each test (at least 24 for each dose level) the influence of varying individual and strain sensitivity is minimized. The results are based on percentage of animals affected, depth of anesthesia and duration of drug action. An added advantage of the method is the requirement of only small quantities of material for a complete test, the necessary amount being at least 100 times smaller than when cats are used. For drugs of the morphin group the results are accurate within $\pm 13.5\%$.

Testing of Local Anesthetics. The application of painful stimuli of uniform, low intensity is made possible by Kniazuk's new instrument. However, normal animals respond only irregularly to such weak stimulation and it is therefore necessary to amplify the visible pain reaction. This can be done by the induction of Sherrington pseudo pain reflexes through the injection of barbiturates. Animals sensitized in such a way respond regularly. It is then easy to differentiate between effective and non-effective concentrations of local anesthetics. By keeping the stimuli just above the threshold value, it is possible to detect and evaluate very weak or highly diluted local anesthetics.

The Anesthetic Action of Bulbocapnine.—HANS MOLITOR (Merck Institute of Therapeutic Research, Rahway, New Jersey). Bulbocapnine, tested with Eddy's tail-squeezer, acts like an analgesic of a potency of about one-fifteenth of that of morphin. If, however, the compression acting as the painful stimulus is instantaneous instead of being gradually increased, as in Eddy's instrument, practically no analgesic action is found in mice and cats. This indicates that the general analgesic effect of this drug is very weak, a result which is in agreement with clinical findings. Bulbocapnine possesses, on the other hand, a marked local anesthetic action which has not been described previously. In a frog nerve-muscle preparation a 5% solution greatly reduces and a 10% solution completely abolishes the reaction to faradic stimulation. On the rabbit's cornea complete anesthesia is produced with a 10%, marked anesthesia (in animals sensitized with Pernoston) with a 2% solution. For nerve-block anesthesia in rabbits and rats a 10% solution is effective. Complete topical anesthesia is obtained with concentrations as low as 2%. The anesthetic action is reversible in all cases. It is rather short in nerve-block anesthesia, where it rarely lasts for more than 1 hour, while the duration in topical anesthesia extends in many experiments over more than 3 hours. Controls performed with a Ringer's solution of the same pH as the bulbocapnine phosphate solution (pH 4.5) show that the anesthetic effect is caused by the drug itself.

Clinical Assays for Male Sex Hormone (Capon Comb Growth Promoting Substance) in Human Urine—Normal Individuals.—L. P. HANSEN, J. F. McCAHEY, and D. SOLOWAY (Departments of Chemistry, Urology, and Anatomy, Jefferson Medical College). With the object of ascertaining correlations between male sex hormone elimination in the urine and various dysfunctions or abnormalities in the human, diurnal specimens of human urine were collected, preserved with chloroform, strongly acidified with hydrochloric acid and extracted with chloroform by prolonged heating on the water bath. The chloroform was separated, dried over neutral salt, and recovered by distillation. The residue was extracted with ether. The ether was removed and the residue was dispersed in olive oil, which was then used for injections into capons. Three capons were used for each test. Each capon received the extract from a 24-hour specimen of urine on each of two successive days. From measurements of the comb the maximum percentage growth was calculated.

Normal individuals of various age periods were studied with the idea of establishing a range of hormone elimination for a given period. In normal children below the age of 10 the response was found to be almost negligible. In normal young men between 20 and 30 the response varied from 21.9 to 30.5%. In composite intermittent day urine of young men of the same age period the response was considerably higher. In men of 50 and above it was definitely lower than in young men, but not invariably so. In composite urine of normal females it was found to be somewhat higher than in boys below 10, but very considerably lower than in young men. Application on the comb of the capon of the extract of urine from individual normal young men, from the extract of composite urine of normal young men, and from composite urine of normal women, produced responses varying from about 15 to 25 times the response obtained by intramuscular injections.

Clinical Assays for Male Sex Hormone in the Urine of Some Abnormal Cases.—JAMES F. MCCAHEY, L. P. HANSEN, and D. SOLOWAY (Departments of Urology, Chemistry, and Anatomy, Jefferson Medical College). Urinary assays for testis hormone were made in a group of individuals presenting certain abnormalities. The hormone was extracted from the urine by the acid-chloroform method. Capons were used for test animals. The results obtained as compared to values found when similar studies were carried out on normal men were as follows:

Cases of Disturbances of Spermatogenesis (Azoöspemia, Neerospermia). The testis hormone elimination was slightly lowered.

Cases of Hypopituitarism. Values obtained ranged from very low to about one-half normal findings.

Cases of Abnormal Secondary Sex Characteristics in Women. Values exceeded those found in normal men.

Arterial, Venous and Cutaneous Blood Platelet Counts in Men and Dogs Under Normal and Abnormal Conditions.—L. M. TOCANTINS (Department of Medicine, Jefferson Medical College). Mean values for the platelet content per c.mm. of blood, obtained from arterial, venous and cutaneous punctures in 40 normal young men: Arterial: 350,000 \pm 13,889. Venous: 310,000 \pm 11,937. Cutaneous: 250,000 \pm 7458.

In a group of 14 normal young men examined during the winter (mean temperature 3° C.) the arterial and venous platelet counts were significantly higher than in a similar group examined during the spring (mean temperature 18.5° C.). There was no significant difference between the cutaneous blood platelet counts in these two groups. There were greater differences between the arteriovenous, arterio-cutaneous and veno-cutaneous blood platelet counts in the winter than in the spring.

In naturally occurring or artificially induced thrombopenias, the initial rise in the blood platelets is detected on arterial blood and coincides with a diminution or return to normal of the mean bleeding time. Cutaneous blood platelet counts may show a thrombopenia for several days after the arterial and venous platelet counts have returned to normal. Platelet counts in arterial blood below 50,000 per c.mm. are almost always accompanied by a prolonged bleeding time.

Platelets are probably utilized as the blood goes through the capillaries. The rate and degree of this utilization will determine in a large measure the relative platelet content of cutaneous and venous blood and eventually, of arterial blood itself. If an adequate supply of platelets is not available from arterial blood (*real* thrombopenia) and a stress (trauma, etc.) is placed on the capillaries and venules, the increased utilization of platelets will result in a deficit in their number, which will be reflected in prolonged bleeding and deficient hemostasis in the affected part. In a *latent* thrombopenia the platelet count of cutaneous and sometimes that of venous blood is below 100,000 per e.mm., but that of arterial blood is often above that number, leaving, under ordinary stresses, a wider margin available for utilization, the mean bleeding time being then normal or only very slightly prolonged.

Electrical Changes in the Spinal Cord.—JOSEPH HUGHES, G. P. McCOUCH, and W. B. STEWART (Institute of the Pennsylvania Hospital and the Department of Physiology, University of Pennsylvania). In the spinal cord, the electrical changes recorded from leads placed longitudinally on the dorsal surface of the cord excited by a single volley in a dorsal root consist of a spike followed by a longer and lower negative complex which is usually succeeded by a prolonged positive wave. The spike has been ascribed to afferent, the later components to internuncial neurons (Gasser and Graham,¹ Hughes and Gasser²). Whether the internuncial potentials arise solely from fibers or also from cell bodies is not known. We believe the results presented here afford a reasonable basis for conjecture. Were their origin confined to axones, the reduction of a second volley by a preceding one would be expected to affect negative and positive components in like degree. In view of the demonstration that the overwhelming majority of afferents terminate upon internuncials (Hoff³), cases of reflex facilitation should be accompanied by an approximately corresponding degree of increase in fiber potentials. On the other hand, if central excitatory state be associated with a negative cell potential and central inhibitory state with positivity of cells, the total electric picture might deviate from such correspondence in proportion to the changes in subliminal excitatory or inhibitory state in the cells contributing to the recorded potential.

Results. In the case of inhibition of the ipsilateral flexor reflex by a preceding volley in a contralateral root, there is a reduction in height of the negative complex approximately proportional to the reduction in the reflex response. Far different is the fate of the positive wave. Instead of a proportional reduction, the positivity is either almost or completely obliterated, even at intervals where negativity is only slightly reduced.

Reflex spacial facilitation is reflected in internuncial potentials, though by no means uniformly to a degree approximating the facilitation observed in the myographic response. Temporal facilitation has shown a five-fold increase in myographic response to the second volley with no increase whatever in the recorded cord potential.

We believe these results suggest the presence of considerable cell potentials in the electrical response of internuncial neurones.

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THE
AMERICAN JOURNAL
OF THE MEDICAL SCIENCES

AUGUST, 1936

ORIGINAL ARTICLES.

STUDIES ON TRANSIENT VENTRICULAR FIBRILLATION.

III. THE PREFIBRILLATORY MECHANISM DURING ESTABLISHED
AURICULO-VENTRICULAR DISSOCIATION.

By SIDNEY P. SCHWARTZ, M.D.,

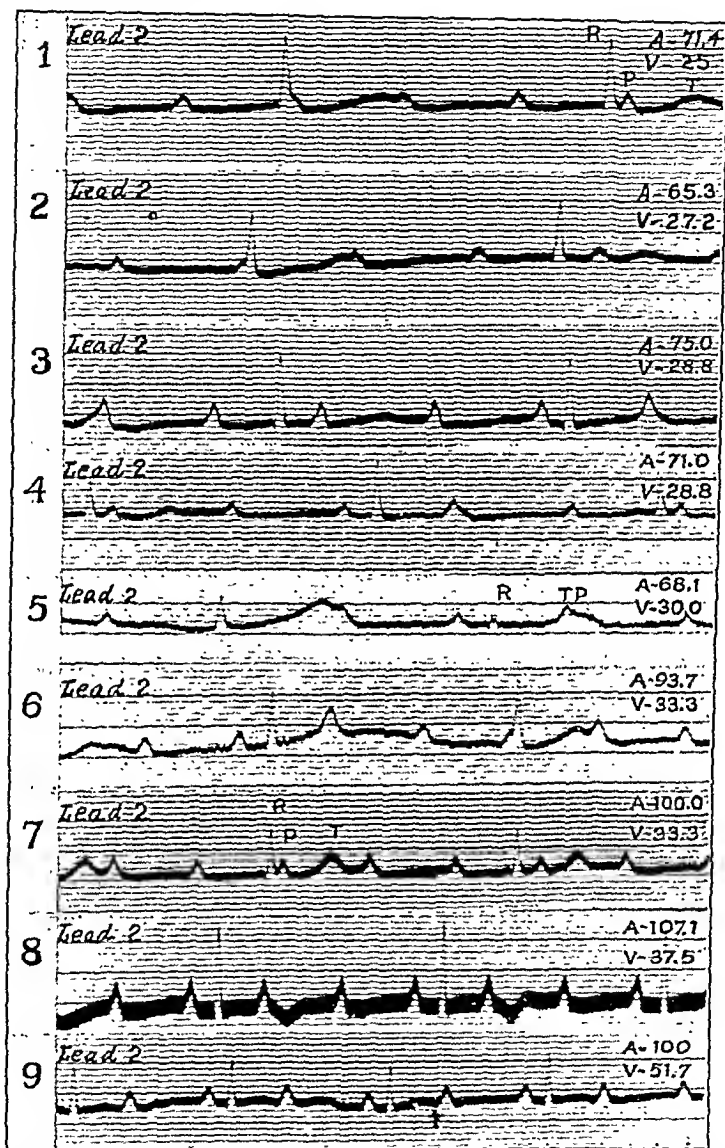
ATTENDING CARDIOGRAPHER TO THE MONTEFIORE HOSPITAL, NEW YORK CITY.

(From the Medical Division of the Montefiore Hospital, Service of Dr Leopold
Lichtwitz.)

THE alterations in the rhythm of the heart preceding transient ventricular fibrillation in the presence of established *A-V* dissociation are often associated with an acceleration of the basic ventricular rate. In 6 patients in whom the ventricular rate was studied prior to the onset of ventricular fibrillation, the average basic ventricular rate was 25 beats per minute without the interposition of premature ventricular beats. The lowest was 17 and the highest 38 beats per minute. The average rate was not influenced by rest or exercise and it was the same during activity, but an average of 6 beats lower during sleep when counts were taken over long periods at a time. Pressure over the carotid artery did not influence the ventricular rhythm and repeated administration of adequate doses of atropin sulphate ($\frac{1}{50}$ th grain) intramuscularly yielded no increase in the ventricular rate.

The Modes of Acceleration of the Basic Ventricular Rate During A-V Dissociation. The acceleration of the basic ventricular rate preceding ventricular fibrillation may be effected through several mechanisms. (A) There may be a simple and progressive shortening of the interventricular periods so that a ventricular rate of 25 beats per minute may rise to 51.7 beats within a short interval (Fig. A 1-9). At such times the impulse pacemaker of the ventricles is very likely within the *A-V* node, for the complexes of the main

ventricular deflections are of the supraventricular type and vary but little from beat to beat.



A. Electrocardiograms (Lead 2 only) showing a progressive increase in the basic auricular and ventricular rates preceding a transient seizure of auricular fibrillation.

(B) On other occasions, a gradual acceleration of the ventricular rate from an average of 37 beats per minute to 65.2 beats, independent of premature beats may take place through a steplike progression of both auricles and ventricles with abrupt changes from com-

plete *A-V* dissociation to partial heart block.¹ Invariably with these abrupt changes there is an accompanying transition of the ventricular deflections from a dextrogram to a levogram and *vice versa* indicating that each successive new pacemaker is somewhere in one of the bundles of the conduction mechanism and alternates with a supraventricular mechanism. When the heart rate has thus been accelerated gradually to a certain level of speed, it is then suddenly interrupted by at first single and then recurrent groups of ventricular oscillations of wide aberrancy that herald the approach of a period of ventricular fibrillation.



B. Electrocardiograms (Lead 2 only) showing the prefibrillatory mechanism in a patient with transient ventricular fibrillation.

(C) Again a very marked increase in the basic ventricular rate is observed to appear abruptly after the ventricles had been already speeded up from an average of 20 to 70 beats per minute, when a greater rate would be ushered in by the interruption of a single extrasystole. This extrasystole was always of a different shape, size and form from both the preceding and succeeding ventricular complexes. It resembled the experimental stimulus with which it is frequently possible to step up the ventricles when isolated from the auricles by the interposition of a well timed beat.

(D) Occasionally a transient seizure of ventricular fibrillation is ushered in by the recurrence of short runs of tachycardia arising

in an ectopic focus of the ventricles, when periods of $A-V$ dissociation and ventricular tachycardias alternate haphazardly for a variable duration until the whole cardiac mechanism is disrupted by the interposition of ventricular oscillations resembling short runs of ventricular fibrillation and then the patient goes into syncope.

(E) Rarely the periods of complete heart block was suddenly disrupted by an irregular heart rate of an average of 160 beats per minute, during which the auricles kept pace with the ventricles as far as rate was concerned but both chambers beat independently of each other. This mechanism was one of an irregular ventricular tachycardia ushering in a period of ventricular fibrillation. It is very likely that many terminal tachycardias preceding ventricular fibrillation arise in a similar manner without any warning, especially if some form of block has been present before or has been induced by a drug.

(F) More often a low basic ventricular rate (from 20 to 30 beats per minute) was increased by the appearance of premature beats of the ventricles, at first coming singly (Fig. C-1) and then in groups of more than one (Fig. C-2, 3, 4, 5, 6). These were observed during partial as well as complete heart block.

The main ventricular deflections of the electrocardiograms during established $A-V$ dissociation were usually of the supraventricular form and were variable in height, shape and form from record to record (Fig. A-5, 6, 7) and in the same record they changed from dextrograms to levograms even in the absence of any increase in the ventricular rate (Fig. B-5).

The T waves of the basic ventricular complexes were usually of the upright form (Fig. A-5, 7) and were preceded by an $R-T$ or $S-T$ interval which was variable in duration, this variation depending apparently upon the rate of the ventricles, that is, the slower ventricular rates showed ventricular complexes with an $R-T$ or $S-T$ interval of longer duration (Compare the $R-T$ interval in 5 and 7 of Fig. A). Both the shape and contour of the $S-T$ interval as well as that of the T waves were invariably influenced by a superimposed auricular contraction. The size, shape and form of the T waves during these intervals were independent of the preceding $Q R S$ complexes. The direction of the T waves remained the same even though the $Q R S$ complexes reversed from dextrograms to levograms.

Deformed Ventricular Complexes in the Electrocardiograms of the Premonitory Period. The most marked changes of both the $Q R S$ complexes as well as of the T waves of the dominant rhythm were observed occasionally during the premonitory period when the block was complete and when the basic rhythm was disrupted by premature ventricular beats which, judging from their shapes, "appeared" to arise from more than one focus (Figs. B-3, 4, 5, and C-4, 5, 6). At such times the main ventricular deflections were



C. Electrocardiograms (Lead 2 only). The prefibrillatory mechanism in a patient with transient periods of ventricular fibrillation during 4-v dissociation. Note the regularity of the auricular waves during the short runs of fibrillation.

extremely variable in height, form and direction from beat to beat. The accompanying *S-T* interval of these deflections was usually shortened and the succeeding *T* waves of the electrocardiograms were occasionally found to have become progressively larger in size from beat to beat, variably deformed and markedly negative.

The deformities of the *T* waves were apparently related to the time of the appearance of the premature ventricular beats following the basic ventricular deflections. The earlier the *S-T* interval of the main ventricular deflection was interrupted by a premature beat of the ventricles, the greater appeared the size and negativity of the *T* waves. For example, in Figure B-4, R_1 is followed by a negative T_1 which is 2 mm. in depth; R_2 is followed by a markedly negative T_2 which is 9 mm. in depth and the same size in width and the next premature ventricular beat is continuous with its ascending limb; R_3 is followed by a negative T_3 which is 11 mm. in depth and from its ascending limb there arises practically one-half of a superimposed premature ventricular beat to be followed also by a markedly positive and large *T* wave (compare also Fig. C-4, 5, 6 and Fig. D, Lead 3).

Frequently the *S-T* interval of a basic ventricular deflection was disrupted by portions of two successive premature beats of the ventricles (Fig. B-5) one so superimposed upon the other as to give a most bizarre picture.

The auricular contractions were not interfered with during the appearance of these superimposed ventricular beats (Fig. C-4, 5, 6).

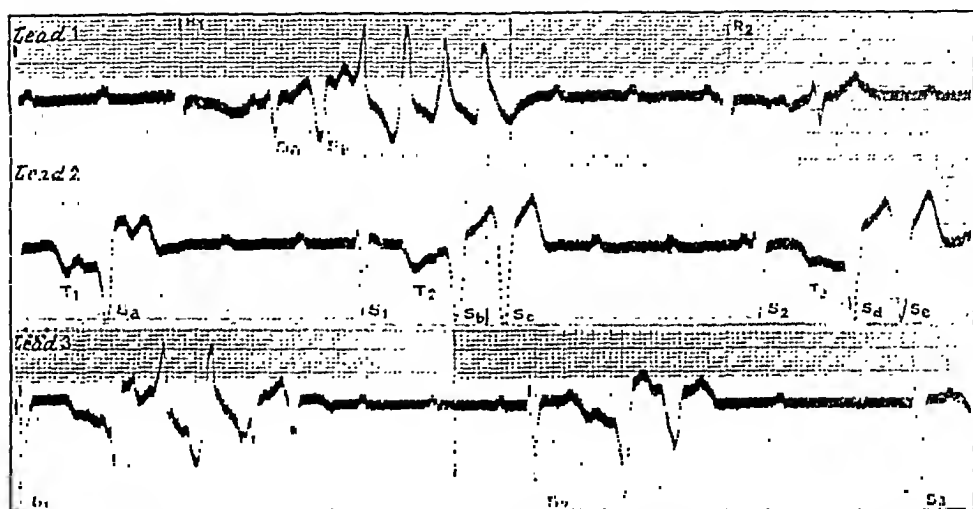
Sometimes, when the alternate premature ventricular beats following the basic ventricular complexes were of the same shape and form from beat to beat and seemed to arise from the same focus in the ventricles repeatedly (Fig. E, Leads 2 and 3) then the deformity of the *T* waves accompanying the main ventricular deflections was uniform and the *S-T* interval preceding it was of the same duration.

The shape, form and direction of the "initial" alternate premature ventricular beats (Fig. C-1, 2) which were the first to disrupt the basic heart rhythm, were at times extremely variable but more frequently, in particular before the development of long syncope seizures, these beats were almost alike for minutes and hours at a time giving the impression that they arose from the same focus in the ventricles (Fig. E, Leads 2 and 3). They were usually opposite in direction to the main ventricular deflection and were uniformly distanced from the foot points of the antecedent ventricular complexes before the onset of a syncope attack (Fig. F).

In hundreds of records obtained of the periods preceding transient ventricular fibrillation in these patients with *A-V* dissociation, not a single instance was encountered in which the onset of syncope was not heralded by premature ventricular beats coming either single, at alternate intervals, or in groups.

The shape of the ventricular oscillations that followed the "initial" premature ventricular beats varied. Sometimes they were opposite in direction to it but most often in the same direction (Fig. C-4).

The frequency and duration of the ventricular oscillations that followed the "initial" premature ventricular beat at any one time was unpredictable. In view of the fact that only the first few of the ventricular oscillations following the "initial" premature ventricular beat could be felt at the pulse, it is very obvious that the greater the duration and frequency of these succeeding ventricular complexes, which were associated with ineffectual contractions of the ventricles, the longer was the accompanying period of syncope.



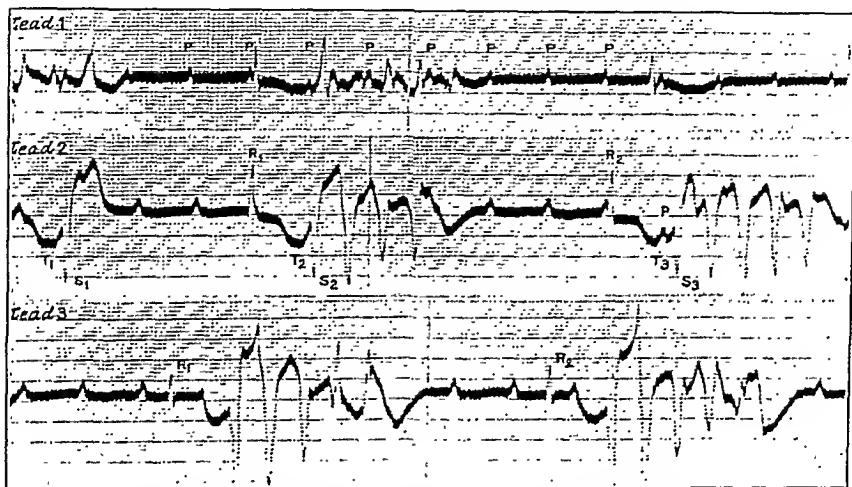
D. Electrocardiograms (Leads 1, 2, 3) of the prefibrillatory mechanism in a patient with A-V dissociation. Compare the basic ventricular complexes and the initial premature beat of this record with that of E.

The duration of the interventricular periods formed by the dominant ventricular complexes during the interruption of the rhythm by these premature ventricular beats was variable from minute to minute. These premature contractions were never observed to have been interpolated. The ventricular cycles succeeding the premature beats were variable, sometimes being equal and sometimes longer than the preceding periods.

Although during this premonitory period none of the recurrent groups of ventricular oscillations could be palpated at the wrist, save for the first few, some could be heard at the apex of the heart while others were neither audible at the apex nor palpable at the wrist. The electrocardiograms of these "audible" groups of beats were more regular in sequence than the latter. The ventricular complexes at such times were sharper and peaked, and although a uniform base line was absent, they remained of about the same size and duration in most of the records obtained, although occasionally their voltage was reduced (Fig. C-5, 6). In these "atypical" ventricular tachy-

cardias the *P* waves were more readily visible on the upstroke of every second beat (Fig. C-3, 4, 6) and what is of particular interest is that frequently these short runs were ended by groups of premature ventricular beats that were distinctly separated from each other by a baseline of short duration, none of which, however, could be palpated at the wrist. Such premature ventricular beats would end the period of tachycardia or would be followed by a postundulatory pause.

The ventricular rates during these tachycardias averaged 200 beats per minute and no such similar cardiac mechanism was recorded for a period longer than 3 seconds.

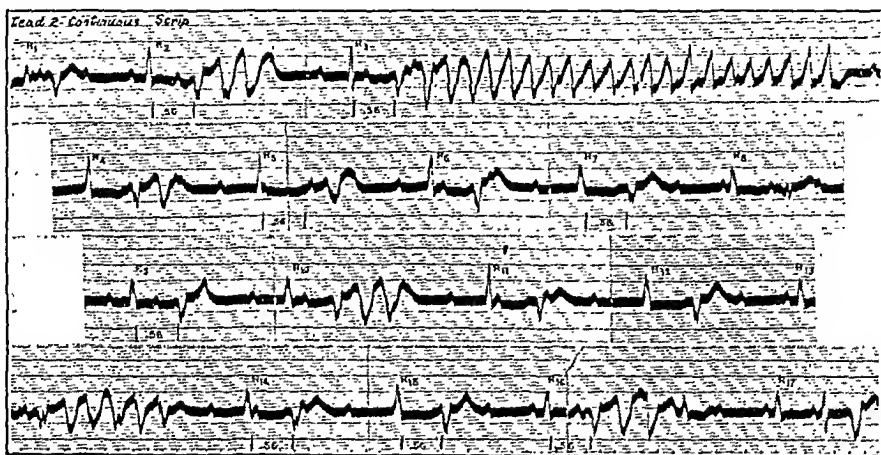


E. Electrocardiograms (Leads 1, 2, 3) showing the prebrillatory mechanism in a patient with A-V dissociation. Compare this record with record D.

The Behavior of the Heart Rhythm Preceding Syncope Due to Standstill of the Ventricles. It is apparent from these records that the alterations in the rate and rhythm of the heart preceding syncope seizures in patients with A-V dissociation and transient ventricular fibrillation are totally different from those patients in whom syncope seizures are due to a slowing of the ventricular rate or complete standstill of the ventricles. In the latter group observations recorded to date reveal that the periods preceding syncope seizures may be appreciated clinically, at times, by the periodic omission of a complete ventricular cycle. This may be followed by the absence of several alternate ventricular cycles, each one of these causing a pause which may be associated clinically with spots before the eyes or short periods of dizziness. More often, the ventricular cycles omitted may be two and three times the duration of normal cycles, especially when there are marked variations in the rate and rhythm of the idioventricular pacemaker so as to cause an inequality of the basic interventricular periods.

Again there may be a progressive increase in the interventricular periods from beat to beat until standstill of the ventricles finally takes place, these progressively lengthening heart pauses resembling very closely Luciani or Wenckenbach periods encountered so frequently in patients with partial heart block.²

Moreover, frequently, the transitional changes from partial to complete heart block resulting in syncope may be associated with a "preautomatic pause,"³ and may be accompanied by a variable standstill of the whole heart at times involving absence of both auricular and ventricular contractions but more often ventricular contractions only.



F. Electrocardiograms (Lead 2 only) showing the initial premature beat to be at the same distance from the basic ventricular complex.

¹ In each of the preceding mechanism in syncope, it is *slowing* of the ventricular rate that precedes the onset of unconsciousness.

The Influence of the Extrinsic Nervous Mechanism on the Auricles and Ventricles During Heart Block. There is some experimental evidence⁴ substantiated by clinically correlated observations⁵ that in certain instances syncope brought on by slowing of the ventricles, with certain exceptions⁶ may be due to an increase in the auricular rate, in contradistinction to the syncope in patients with ventricular fibrillation in whom the auricular rate usually remains the same before the seizures. There can be no doubt that in some of these patients this acceleration of the auricular rate is in some way related to reflex stimulation of the extrinsic nervous mechanism of the heart.⁷ These facts are emphasized at the present time because very recently Shookoff⁸ reported a patient in whom during the presence of auricular fibrillation, pressure over the right common carotid artery (indirectly stimulating the vagus nerve to the heart) resulted in an irregularity considered to be that of ventricular fibrillation. The records published by him resemble more closely some of the large coarse irregular waves of impure flutter encoun-

tered either during so-called coarse auricular fibrillation or normal rhythm, several examples of which may be found in Geraudel's studies⁹ and considered by him as "false ventricular fibrillation."

Ventricular fibrillation once established, even for brief periods, is practically never interrupted by a supraventricular complex before the fibrillatory process ends spontaneously and then only when a postundulatory pause does not precede restoration of the basic rhythm, does a premature beat or a markedly aberrant ventricular complex resembling it, end a seizure. Furthermore, as we have pointed out previously, in the thousands of brief periods of ventricular fibrillation that we have recorded, none have been observed to appear without at least one "initial" premature ventricular beat preceding the ventricular period during which fibrillation sets in. For these reasons we believe that Shookoff's case, the only clinical instance published to date in which reflex stimulation of the vagus nerve is held responsible for initiating transient ventricular fibrillation, may be based on a misinterpretation of the electrocardiograms recorded.

Summary and Conclusions. The clinical and electrocardiographic manifestations in 6 patients with *A-V* dissociation who exhibited recurrent syncopal attacks due to transient ventricular fibrillation have been correlated.

In each instance it was determined that the alterations in the rhythm of the heart preceding a period of ventricular fibrillation were characterized by an acceleration of the basic ventricular rate of the ventricles.

The acceleration of the ventricular rate preceding ventricular fibrillation in patients with *A-V* dissociation was effected through: A, A simple and progressive shortening of the interventricular periods; B, A steplike progression of both auricles and ventricles with abrupt changes from partial to complete heart block and *vice versa*, each alteration resulting in a further acceleration of the ventricular rate; C, the interposition of a single extrasystole changing a slower rhythm to a faster one with a concomitant change in the pacemaker of the ventricles; D, recurrent short runs of tachycardia arising in an ectopic focus of the ventricles and alternating with the periods of heart block; E, a tachysystole in which a rapid auricular rate kept pace with a rapid ventricular rate before fibrillation disrupted the whole cardiac mechanism and finally F, isolated premature beats of the ventricles which appeared in rapid succession and accelerated the heart before the cardiac mechanism responsible for syncope had set in.

On the basis of these correlated observations, it is fair to assume that a diagnosis of transient ventricular fibrillation may be suspected in a patient with *A-V* dissociation and syncopal attacks if any of these cardiac mechanisms are observed to appear either prior to or subsequent to syncopal seizures.

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BLOOD REGENERATION IN PATIENTS WITH HEMATEMESIS OR MELENA FROM PEPTIC ULCER, TREATED WITH THE USUAL ULCER CURE AND WITH THE MEULENGRACHT TREATMENT.

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IN July, 1931, Meulengracht altered the treatment of patients with hematemesis or melena in this department. Previously, such patients were given the usual "ulcer cure." After a few days' fasting, they had cold tea or oatmeal gruel, advancing very slowly through milk and milk soups with sago, ricemeal, etc., to the "purée diet" which was generally attained after about 4 weeks. Meulengracht now gave this purée diet in its full extent from the first day of admission, which often meant from the first day of bleeding. This is a well-balanced diet which includes meat, fish, vegetables, fruit, potatoes, in fact all sorts of food, finely minced in the form of forcemeat, mashed potatoes, puréed vegetables, fruit soups, jellies, and so on. In addition, iron was given, and an aperient (*e. g.*, cascara). Meulengracht was induced to make this alteration chiefly from clinical observation and from the well-known experiments of Whipple, Hooper and Robscheit,³ in which they showed that anemic dogs regenerate blood much better on certain diets, especially meat and liver, than when fasting or fed on carbohydrates and milk. There is no reason to suppose that human beings should react differently to hemorrhage.

The object of this communication is to show the difference in blood regeneration before and after Meulengraecht's treatment was introduced.

Methods. The following hemoglobin estimations and red cell counts were made upon patients admitted for hematemesis or melena. In all patients, gastric or duodenal ulcer was supposed to be the source of the hemorrhage, patients with cancer of the stomach or cirrhosis of the liver being excluded, even though given the same treatment.

Blood was taken for examination about once a week. During the first week more examinations have been made in most patients.

Hemoglobin estimations were all made with the same Autenrieth-Königsberger hemometer. The same apparatus has been used daily since 1917; it has been standardized twice (in 1918 and 1934) with the oxygen capacity method ($100\% \text{ Hb} = 18.5 \text{ cc. O}_2$). The correction has not altered measurably. Several times examination of series of normal persons has shown this standard to give a color index about 1. On each sample two readings were made and an average given. The red cell count was made in a Bürker-Türk chamber, 10 big squares being counted, making the cipher for multiplication 5000. All estimations of hemoglobin and counting of red cells were made on venous blood from the cubital vein, 3 to 4 cc. being stabilized by 3 drops of saturated solution of sodium oxalate. Correction for this surplus fluid has not been made. In all individual samples the hemoglobin estimation and the red cell count were made from the same blood by the same person, a technical assistant. About 95% of all determinations were made by one assistant, Miss Lundgreen, the rest were made by another technical assistant, Miss Norman-Hansen, but no difference could be detected between the values obtained by the two.

Patients on the Old Ulcer Cure. Most of these patients' records date from 1929 to 1931, a few from later years. They were all given the aforementioned ulcer cure, many were fasted for a few days; about 4 weeks after admission the purée diet was given, and most of the patients have had some iron medicament a little later.

Patients on Purée Diet and Iron. These patients all date from 1931 to 1935. The patients were given the purée diet from the first day of admission and also iron from the first day (ferrosi lactat., centigrams 50×3). The patients have not been pressed to eat but have followed their own appetite.

Results. As an example of how much this consumption of food could amount to, I give one day's experience, although, to be sure, this patient ate well above the average: A man, aged 37, from April 11, 1935, repeatedly had melena or hematemesis. On April 12, he was admitted to hospital and given the purée diet and iron, and on April 14 a transfusion of blood (300 cc.). On April 15, he had hematemesis for the last time. This day (before the hematemesis) his Hg % was 30 and his R.B.C. 1.42 millions. The next day, April 16, his consumption of food as controlled by the nurses was: In the morning: 150 gm. oatmeal porridge; for dinner (at 1 o'clock): fruit soup, boiled forced-meat-balls and green-pea purée and in the evening; a soft-boiled egg and a little piece of white bread. Also, in the course of the day he drank 1 liter of milk and 1 glass of churned milk with cream and consumed 4 oranges, 2 bananas and

2 biscuits. The day after, April 17, his Hg % was 21 and the R.B.C. 0.87 million, but 19 days later, he had reached 67% and 3 millions.

One Patient Treated With Both Cures Successively. This patient was admitted 4 times, twice in 1928 and twice in 1932. The first time (January, 1928) she apparently had lost blood from her bowels without noticing it; she was sent in to be treated for anemia but had really regenerated her blood quite well on her usual diet. The second time she had melena and was treated with the ulcer cure (July to September, 1928). The third time (January, 1932) she had a hematemesis and was treated with the purée diet, but insufficient blood examinations were made to estimate her regeneration. The fourth time (September, 1932) she had melena and was given purée diet and iron. The curves of regeneration for the second and fourth admissions are shown on Fig. 1.

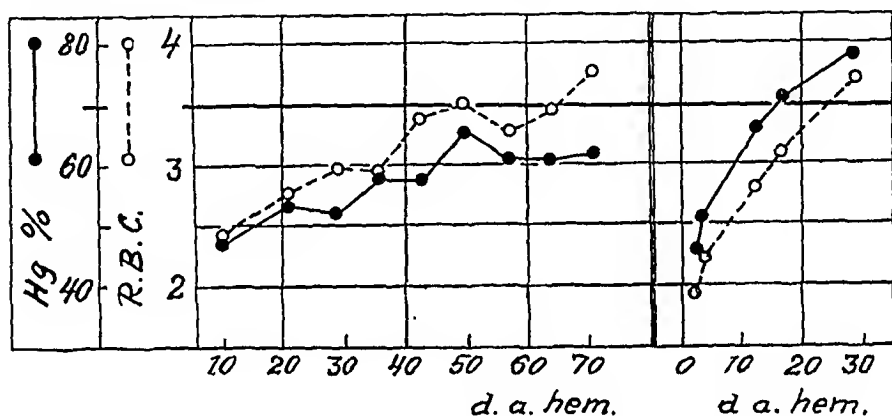


FIG. 1.—Woman, aged 48 (in 1928). To the left, Hg % and R.B.C. on ulcer cure. To the right, Hg % and R.B.C. on purée diet and iron. Ordinate: Hg % and R.B.C. Abscissæ: Days after hemorrhage.

Comparison Between the Two Groups. A comparison between the two groups can only be valid when the severity of the hemorrhage is taken into account. Even then, the individual's inherent ability to regenerate remains an unknown factor. For comparison, I have selected from each group those 10 patients whose red blood cell count on the first examination after admission was nearest to 2.5 millions. This examination was made on the first to the third day after admission. The patients were admitted on the first to the seventh day after the first bleeding. As far as possible such patients have been omitted where there is not at least 24 hours between the last known hemorrhage and the first blood examination. The average time from the first hemorrhage to admission is, for the ulcer cure group, 2.4 days and for the purée diet group 2.2 days and the average time from the first hemorrhage to the first blood examination is 4.4 and 3.9 days, respectively.

The two groups, besides, are comparable as to age and sex. No patient had known complications of any sort, or was given transfusion of blood or had hematemesis or apparently fresh melena after the first blood examination. Only a few, indeed, had more than one known hemorrhage.

TABLE 1.—AVERAGE BLOOD VALUES FOR PATIENTS ON ULCER CURE AND ON PURÉE DIET AND IRON.

	Hg % on adm.	R.B.C. on adm.	Hg % 20 days later.	R.B.C. 20 days later.
10 patients on ulcer cure	47.5 \pm 2.1	2.43 \pm 0.10	50.0 \pm 1.9	2.80 \pm 0.09
10 patients on purée diet and iron	50.0 \pm 2.1	2.42 \pm 0.11	68.4 \pm 2.6	3.45 \pm 0.12
Difference	2.50 \pm 2.9	0.01 \pm 0.15	18.4 \pm 3.2	0.65 \pm 0.15

In the ulcer cure group, 4 patients had hematemesis, in the purée diet group 6; the other patients had only melena. The average Hg % estimations and R.B.C. counts in the two groups will be seen from Table 1, where the values from the first blood examination are compared to the values found 20 days later.

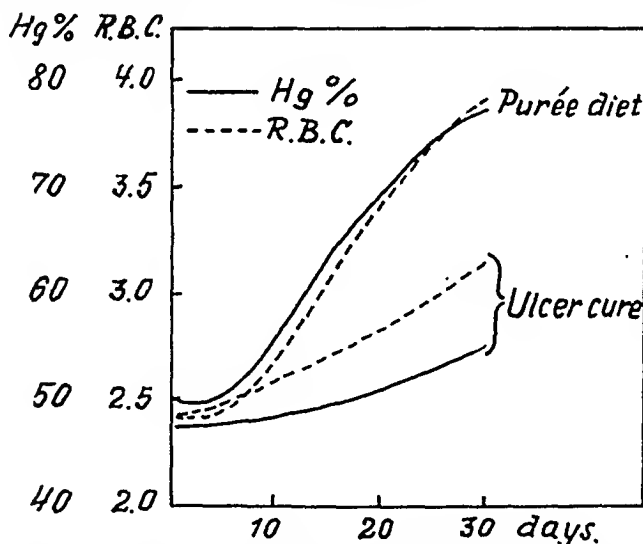


FIG. 2.—Balanced average curves of Hg % and R.B.C. count in patients on ulcer cure and purée diet. Upper curves: Patients on purée diet. Lower curves: Patients on ulcer cure. Ordinate: Hg % and R.B.C. Abscisse: Days from first examination on admission.

Thus the difference between the two groups on admission is less than the medium error. The difference in the values for the two groups on the 20th day for Hg % is 18.4 ± 3.2 ; *i. e.*, 5.6 times the medium error and for the R.B.C. 0.65 ± 0.15 ; *i. e.*, 4.3 times the medium error. The highest Hg % on the 20th day in the ulcer-cure group is 57; only 1 in the other group is as low as

that. Fig. 2 presents balanced average curves of Hg % and R.B.C. in the two groups.

Hemoglobin and Blood Corpuscle Regeneration Compared. On the purée diet, the curves for hemoglobin and red blood cells follow each other very closely, the color index during the whole period being very near 1. In many patients, especially those who bled more severely than did the cases in this paper, it has even been well above 1. The patients on ulcer cure, on the other hand, regenerate the hemoglobin markedly slower than red corpuscles. Color index during the whole time of observation is low; on the 20th day, for example, 0.89 against 0.99 for the patients on purée diet.

The effect of iron cannot be estimated from our material, but Gram¹ has found that 20 patients on purée diet and iron regenerated on an average in 10 days 15.4% of the deficit (*i. e.*, lowest normal hemoglobin value for the sex minus hemoglobin on admission), or expressed in absolute values, Hg 6.1%. This coincides well with the 5% rise found for our patients in the first 10 days. For patients on purée diet without iron, Gram found a rise of 3.3% hemoglobin in the first 10 days. As will be seen on the curve, patients on ulcer cure showed no perceptible regeneration in the same time. It seems thus—and it is also our impression from a number of patients not quite suitable for comparison in the way here used—that food alone is of definite value for the regeneration of the blood whether or not the effect is supported by giving iron too.

Conclusions. Patients who have lost blood, apparently from peptic ulcer, on full purée diet and iron regenerate their blood much more quickly than those on "ulcer cure." This is well illustrated in the patient who was treated twice for a hemorrhage of about the same degree of severity. This applies especially to the hemoglobin regeneration, as patients regenerate their blood with a lower color index on the ulcer cure than on the purée diet.

Besides the subjective better feeling of the patients, and the better clinical improvement, obvious to both doctors and nurses, but not to be expressed in figures, the better regeneration of the blood supports the lower mortality in maintaining the superiority of the Meulengracht² treatment over the old ulcer cure in patients with bleeding ulcer. As in Whipple and his coworkers³ experiments on dogs, adequate food has proved its value in regeneration of the blood. These observations do not indicate whether or not some elements in food given are more effective than others, nor whether the effect depends more on quantity than on quality.

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EXPERIMENTS WITH "DEPEPSINIZED" HUMAN GASTRIC JUICE IN THE TREATMENT OF PERNICIOUS ANEMIA.

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IN 1932 Roger Morris and associates¹ announced that they had demonstrated in normal gastric juice a "specific hematopoietic hormone" capable of producing, when parenterally administered, significant remissions in pernicious anemia. The gastric "hormone" hypothesis set forth in this and subsequent papers^{2,3} was criticized by Minor and Castle⁴ and others.^{5,6,7} Intramuscular injection of gastric juice might result in a "specific reaction" between the "intrinsic factor" of the juice and the muscle tissue of the recipient. Furthermore, the irritant action of injected gastric juice might result in a purely non-specific hematopoietic stimulation (comparable to that of arsenic), which, if true, would prove nothing as to its alleged hormonal nature and nothing as to a specific relationship with the disease.

It may be important to point out that in the reports of Morris and his co-workers there are only two really significant responses recorded from the injection of human gastric juice—the rest being the results of injection of swine gastric juice obtained by a method not described (presumably "pressed" stomach of slaughtered animals). Can it be that this swine gastric juice was extracted from animals not sufficiently fasted to remove all possibility of specific interaction products? Even if these animals were properly fasted, it might be that the "pressed" juice would represent nothing more nor less than a sort of liquid "ventriculin."

Later workers either completely failed to duplicate Morris' results (Wilkinson⁵ and Vladoš⁶) or obtained somewhat different results pointing to a different interpretation (Fouts and Zervas⁷). The later workers found that fresh gastric juice was inert and that ice-box storage for 2 months or more resulted in the development of some degree of potency apparently from some kind of slow "interaction" within the stored juice.

More recently Greenspon⁸ presented evidence purporting to prove that the "antipernicious anemia factor" in the stomach (Castle's intrinsic factor) is the only fundamental one and that no extrinsic

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or food factor and no interaction product need be considered. Greenspon's experiments led him to conclude that pepsin is antagonistic to this intrinsic factor, which may preserve its potency outside the living organism (*a*), only if protein is present to adsorb pepsin and thus prevent alleged peptic destruction of the intrinsic factor, or (*b*), if other means such as alkalization, chilling, and isoelectric precipitation of pepsin are employed to inhibit pepsin or remove it from the field of action.

Greenspon's experiments, as reported, do not seem to be entirely conclusive. His ventriculin experiment is difficult to criticize. It should be pointed out, however, that according to Greenspon, since "ventriculin contains native pepsin" the addition of extra pepsin would seem to be unnecessary for the inactivation of ventriculin if optimum acidity, moisture, and temperature conditions were provided. We plan to test this corollary of Greenspon's thesis which, if true, would tend to strengthen rather than weaken his apparent proof of the destructive action of peptic activity on ventriculin.

Greenspon's next experiments with his preparation of "depepsinized" hog gastric mucosa certainly seem to constitute good grounds for his conclusion that "peptic activity destroys the antipernicious anemia principle and that hydrochloric acid alone does not." Greenspon's observations (on 2 cases) must be extended and confirmed, however, before one can exclude the possibility of other factors having been responsible for the observed results.

His final experiments with the feeding of normal human gastric juice, "peptically inactivated," and with the parenteral injection of concentrates of normal "depepsinized" human gastric juice to patients with pernicious anemia are of especial interest and importance. The criticisms that come to mind regarding these experiments, as reported, are as follows: 1st, the normal human gastric juice donors should have been submitted to at least a 12-hour fast and gastric lavage should have then immediately preceded the collections to eliminate as far as possible all food residues and, 2d, the pernicious anemia recipients of this normal gastric juice, although treated "in the morning on an empty stomach," should have also received gastric lavage before the administration of the juice and should have again received gastric lavage before any food was allowed "4 hours later"—which is too brief a fast-period as Minot has pointed out.*

We have attempted to review some of Greenspon's experiments with these "criticisms" in mind. Although our work, to an even greater extent than his, is open to the objection of "too few cases" and "insufficient observations," it seems none-the-less worth recording as a small part of the data which must eventually be collected and sifted before any sound conclusions can be reached.

* Personal communication.

Methods. The 3 patients with pernicious anemia used in this study were proven cases, in relapse, with red cell counts between 1.4 and 2.3 million and hemoglobin values from 40 to 58% (Sahli). These patients were hospitalized on a meat, broth and iron-free diet during the course of these studies.

Gastric Juice Concentrates for Parenteral Administration. "Depepsinization" of gastric juice was carried out by the method of Fenger and Andrews⁹ as recommended by Greenspon.⁸ The gastric juice concentrate used in Experiment 1 was prepared in as close accordance with the latter's technique as his brief description of the process permitted. In subsequent experiments (5, 6 and 7), Greenspon's method was closely followed except that after isoelectric precipitation of pepsin and its removal by centrifugalization, the clear supernatant fluid was poured into large pans and reduced to a moist flaky residue by exposure to a current of air never exceeding 33° C. in temperature. This method was found simpler and more rapid than concentration *in vacuo*. The moist residue was then taken up in 30 to 50 cc. of distilled water, treated with alcohol and reconstituted *in vacuo* at 35° to 37° C. to a volume suitable for intramuscular injection. pH values were determined by means of a potentiometer. Each concentrate was tested for sterility.

In Experiments 3 and 4 attempts were made to concentrate gastric juice by lyophilization.¹⁰ This process offers the advantage of intense cold and dryness, both of which inhibit peptic activity.

The acetone soluble fraction used in Experiment 4 was prepared by the addition of acetone to the depepsinized lyophilized concentrate. A dense white precipitate formed and settled out rapidly. The supernatant fluid was concentrated *in vacuo* to 15 cc. and injected. Opportunity to test the acetone-insoluble fraction has not yet occurred.

Normal gastric juice was obtained from ward and clinic patients with normal blood counts, normal gastric acidity and without evidence of tuberculosis, syphilis or other active infection. In all cases the fasting specimens were discarded and thorough lavage with dilute solution of sodium bicarbonate preceded collection of the juice. The secretions were drained for about 3 hours; suction siphonage was employed in most cases and the collecting bottles were packed in cracked ice. Resort was made to histamin stimulation of gastric secretion in "normal" cases only.

It may be incidentally noted that good yields of pepsin were obtained from normal gastric juice (Experiments 4, 5 and 7); however, pepsin was absent (Experiments 1 and 3) or scanty (Experiment 6) in the gastric juice of patients suffering from pernicious anemia. This concurs with the findings of other investigators.¹¹

Gastric Juice Preparation for Oral Administration. Gastric juice for "peptic inactivation" and feeding was secured from 4 "normal" patients. Greenspon's technique was followed closely and in addition each fasting donor underwent preliminary gastric lavage.

EXPERIMENT 1. Mrs. F. (Medical clinic record, 3520535), a typical case of pernicious anemia in relapse, was both donor and recipient in this experiment. After preliminary observation and a week of meat-free diet she received an injection of a concentrate (11 cc.) representing an original volume of 200 cc. of fasting "depepsinized" gastric juice obtained from her own stomach during the preceding week. Reticulocyte fluctuation, for 10 days before and 6 days thereafter, varied between 0.2% and 1.3%. We considered this a completely negative result.

This experiment was undertaken with the thought that if Morris'

so-called addisin produced merely non-specific irritation effects rather than true "hormonal stimulation" there would be no *a priori* reason why pernicious anemia juice might not be as effective as normal juice. Our negative response to pernicious anemia juice seemed to be in line with Morris' hypothesis.*

EXPERIMENT 2. This same patient received, after 14 hours' fasting and immediately preceded by gastric lavage, 500 cc. of pooled normal "peptically inactivated" fasting gastric juice by stomach tube. Food was then further withheld for 5 hours and before any food was administered gastric lavage was repeated to remove any possible residue of the instilled juice. Three days later another 500 cc. of similar normal gastric juice was administered by tube with identical precautions. The reticulocyte level showed a slight increase to 4% on the third day after the first gastric juice feeding (*i. e.*, the day of the second gastric juice feeding). This reached a peak of 5% one day later and then subsided to less than 1% during the following 6 days. At the end of this experiment, 6 days after the second gastric juice feeding, the hemoglobin, red cell count and reticulocytes were a trifle lower than before any of these experiments were begun. This patient's blood picture throughout was in the neighborhood of 1,800,000 red blood cells and 45% hemoglobin. Subsequently (6 days) a reticulocyte rise to 8.2% was obtained from an experimental fraction of liver extract furnished by and administered at the request of Dr. Randolph West. Finally, after this reticulocyte wave had partially subsided, and hemoglobin regeneration was well underway, parenteral administration of a known potent commercial liver extract produced a slight secondary reticulocyte response (8.5%) which was followed by the usual complete hematologic recovery characteristic of Addisonian anemia. Dr. West's fraction was apparently a potent one, because 11 days after its administration the hemoglobin had increased from 40 to 62% (Sahli).

Conclusions: There was a questionably significant rise in reticulocytes which reached a peak on the fifth day after gastric juice feeding was initiated. This was followed by little or no change in the patient's red cells and hemoglobin during the following 2 weeks. We interpret this as uncertain evidence of a minimal response. The normal gastric juice which apparently produced this questionable response was pooled material less than 4 days old and treated throughout according to Greenspon's technique.

We cannot accept this evidence as proof of anything. We have not infrequently observed spontaneous reticulocytosis of this magnitude. Furthermore, even though we took special precautions to to exclude food factors from both donor and recipient, it is obvious

* This experiment, carried out during February, 1936, was similar to one reported subsequently by Goldhamer.¹² Incidentally our result differs from Goldhamer's in that he obtained what he considered to be evidence of some intrinsic factor in the pernicious anemia gastric juice which he employed.

that prolonged starvation of both would be necessary to approximate this objective.

EXPERIMENT 3. Mr. Q. (Medical Clinic record, 304100). a typical case of pernicious anemia in relapse, was the recipient and in part the donor too in this experiment. An attempt was made to concentrate gastric juice from 3 pernicious anemia patients in relapse by lyophilization. Owing to difficulty in securing a sterile finished product* the contaminated lyophilized concentrate of an original amount of 248 cc. of pernicious anemia gastric juice was subsequently pooled with 130 cc. of fresh similar pernicious anemia juice and the mixture concentrated (and incidentally sterilized) by the method used in Experiment 1. The finished concentrate, amounting to 10 cc. (derived from 378 cc. of pernicious anemia gastric juice), was injected. The patient developed a rather severe local and systemic reaction. The highest pre-treatment reticulocyte figure during 2 weeks' preliminary observation was 2.1%. The day after the injection the reticulocytes numbered 3%. Subsequently there occurred a slight wave of reticulocytes which reached a peak of 4.7% on the twelfth day after the injection. During this period, however, the red cells and hemoglobin declined moderately and the patient was clinically worse.

Our conclusions from this are identical with those on Experiment 1. We obtained no evidence of activity from pernicious anemia gastric juice injections. We are inclined to believe that the slight reticulocyte rise noted in this experiment was not significant. The process of "lyophilization" employed in this and the following experiment may make them inadequate "controls" as far as Greenspon's, Goldhamer's and Morris' techniques are concerned.

EXPERIMENT 4. This same patient received (intramuscularly) a concentrate (11 cc.) of the acetone soluble fraction of lyophilized normal fasting human gastric juice representing an original volume of 600 cc. On the fourth day following this injection the reticulocytes rose from a pre-injection level of 1.4% to 3.5% and then declined to the pre-injection level. A week later the patient's red cells and hemoglobin were unchanged.

Conclusions. Either lyophilization destroyed the (alleged) hematopoietic activity of the normal "depepsinized" gastric juice employed in this experiment or none was present in this fraction.

EXPERIMENT 5. This same patient was given (intramuscularly) a concentrate (12 cc.) representing an original volume of 700 cc. of normal "depepsinized" fasting human gastric juice obtained during the preceding week. The highest reticulocyte figure after this injection was on the fourth day (2.3%) and 20 days after the injection the red cell count and hemoglobin were unchanged (1.9 million and 45% respectively). At this juncture potent liver extract injections produced, after 6 days, a reticulocyte crisis of 29%.

* The process of lyophilization does not sterilize previously contaminated material.

Conclusions. This experiment fails to confirm the results of Greenspon and incidentally of Morris and co-workers and of Conner.¹³

EXPERIMENT 6. Mr. S. (Medical Clinic record, 3622319) was a typical case of pernicious anemia in relapse. Throughout a preliminary period of observation of 12 days in the ward on a meat-free diet the red cells and hemoglobin were constantly in the neighborhood of 1.9 and 40% respectively. The reticuloeytes, however, showed a slight spontaneous rise from an average of 1% to a peak of 5.4% without any treatment. After this spontaneous reticulocyte wave had subsided the patient received a parenteral injection of 10 cc. of his own concentrated "depepsinized" gastric juice representing a total volume of 320 cc. collected during the preceding 10 days. Following this injection, by 4 and 8 days respectively, there were two peaks of reticulocytosis of 4.5% and 5.3% each, without any significant change in the rest of the blood picture or in the clinical condition of the patient.

Our conclusions from this experiment are similar to those in Experiment 1 (and 3). We thought it best in these experiments with pernicious anemia gastric juice to follow Greenspon's directions regarding the inactivation and removal of pepsin, even though we could demonstrate little or no pepsin in the specimens obtained from our pernicious anemia patients.

EXPERIMENT 7. This same patient received a concentrate (10 cc.) representing an original volume of 500 cc. of normal depepsinized fasting human gastric juice collected within the preceding week. During the following 8 days the reticulocytes did not go above 2.4% which is less than had been previously noted during the control period. Subsequently potent commercial liver extract injections were followed by the typical hematologic and clinical recovery characteristic of Addisonian anemia. The patient was uncoöperative and left the ward after 6 days of potent liver therapy when his reticulocyte rise was well underway (12%) but before the peak. Three weeks later his hemoglobin was 84% and red cells were 4 million.

Conclusions. This experiment failed to confirm the results of Greenspon and Morris.

Discussion. Contrary to the results of Goldhamer,¹² we obtained no conclusive evidence of the presence of "intrinsic factor" in pernicious anemia gastric juice obtained from and readministered to 3 patients in relapse phase (Experiments 1, 3, and 6). These negative results might be interpreted as evidence against the "non-specific irritation" hypothesis advanced by Castle and Minot to explain Morris' results with so-called addisin. No conclusions, however, may be drawn because we failed also to obtain a significant response from similar injections of normal gastric juice concentrates (Experiments 4, 5 and 7).

Contrary to the results of Morris and co-workers, we obtained no significant responses from intramuscular injections of normal fasting human gastric juice concentrates administered to two differ-

ent patients in relapse phase of pernicious anemia. Our concentrates of normal juice were prepared according to Morris' technique plus the "depepsinizing" procedures of Greenspon in most instances (Experiments 5 and 7). In one instance in this normal juice group, however, we tried a "lyophilized" concentrate (Experiment 4), which was equally ineffective. In no instance in this series of experiments did we observe the marked leukocytosis, the nucleosis, or the increase of nuclear particles in red cells reported by Morris and Greenspon. Platelet increase was observed in one instance (Experiment 3).

Contrary to the results of Greenspon we obtained no conclusive responses from either the feeding (Experiment 2) or the injection (Experiments 5 and 7) of "depepsinized" normal fasting human gastric juice, prepared according to Greenspon's description, but obtained and administered with rigid care to exclude as far as possible extrinsic food factors in both donors and recipients. While our experiments do not actually disprove any of the conclusions of Morris or Greenspon, and particularly do not touch seriously upon Greenspon's apparent demonstration of peptic antagonism toward intrinsic factor (which we are not prepared to question on the basis of our work), they do cast doubt upon their hypothesis in so far as it excludes Castle's "extrinsic factor" and "interaction products."

Summary. 1. In 3 patients in relapse phase of pernicious anemia intramuscular injections of "depepsinized" concentrates of fasting gastric juice obtained from themselves failed to produce significant reticuloocyte responses.

2. In 1 patient in relapse phase of pernicious anemia the oral administration (of 1000 cc. in 2 doses) of "peptically inactivated" normal fasting human gastric juice failed to produce a truly significant reticuloocyte response (*i. e.*, no greater reticulocytosis than we have observed to occur spontaneously in relapse phases of pernicious anemia).

3. In 2 patients in relapse phase of pernicious anemia the intramuscular injection of depepsinized normal fasting human gastric juice concentrates failed to produce significant reticuloocyte responses.

Conclusions. Our experiments fail to substantiate the results and hypotheses of Morris and co-workers and of Greenspon, as regards the sole importance of "intrinsic factor." While entirely negative, our experiments constitute no grounds for disbelief in Castle's fundamental "conditioned deficiency" concept of pernicious anemia. We believe that Greenspon, although possibly right in his conclusion that peptic digestion destroys "ventriculin," has not proven the rest of his hypothesis regarding the complete unimportance of Castle's "extrinsic" factor and "interaction product" mechanisms.

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THE EFFECT OF AMIDOPYRIN UPON THE RED, WHITE AND POLYMORPHONUCLEAR BLOOD CELLS OF A SERIES OF 100 PATIENTS.

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In a previous paper,¹ 2 patients were reported with agranulocytosis which developed during the routine administration of amidopyrin. My first cases of agranulocytosis attributed to amidopyrin medication were observed on February 4, 1933 (reported at the February Staff Conference of this hospital) and in June, 1933. Both were reported before the Clinical Society of the New York Polyclinic Medical School and Hospital in November, 1933. Since that time, 2 more cases have been observed in private practice and 2 others in consultation.

The literature on the subject is now voluminous. To date, however, there has not appeared any statistical analysis of the effect of amidopyrin upon the hematologic findings of a large series of patients. Although divergent views on the subject exist, it is believed that enough evidence has been published to indicate that amidopyrin bears some causal relationship to agranulocytosis.

A review of the literature is unnecessary, because this was recently analyzed by Kracke,² who collected reports of 172 cases attributed to drug therapy, of which 153 were probably caused by amidopyrin.

Vaughan³ showed that the ingestion of food to which a patient is sensitive may produce leukopenia. This, however, involves all of the white blood cells and is not a true agranulocytosis. Squier and Madison⁴ demonstrated skin sensitivity to amidopyrin by patch testing of 2 or 3 patients who had recovered from agranulocytosis. On the other hand, Benjamin and Biederman,⁵ using patch methods, found no evidence of the allergic state in their patients. Taussig⁶ reported a case of urticaria developing after a 5-gr. dose of amidopyrin, although a few months previously the patient had taken it without any toxic effect. The author has observed 3 cases of urticaria which developed during amidopyrin medication. In these cases, the urticaria appeared after only a few doses of amidopyrin. The exact method by means of which amidopyrin acts to produce agranulocytosis is still in doubt. Kracke² discussed the different theories and the reader is referred to his monograph for a more detailed report.

The present study was undertaken to determine (1) the frequency of the occurrence of agranulocytosis in a series of 100 patients treated with amidopyrin, and (2) any change in the red and white blood cell counts, or polymorphonuclear counts, of patients who were treated with amidopyrin but did not develop agranulocytosis. This was done in an effort to determine if agranulocytosis might be due to drug idiosyncrasy or if leukocytic changes occur with any regularity during the course of amidopyrin medication.

In some cases, magnepyrin, a preparation containing a mixture of amidopyrin (2½ gr.) and magnesium carbonate (4 gr.), was used, usually 3 or 4 of these tablets being administered daily for varying intervals. The other patients were given amidopyrin (5 gr.), 3 or 4 times daily. The patients each received a mean daily dose of 13.08 gr. and a mean total amount of 1098 gr. of amidopyrin during a mean interval of 84.36 days.

Patients with rheumatoid and miscellaneous arthritis (including mixed and osteoarthritis) were selected for study whenever they were admitted to the clinic. A complete blood count, sedimentation rate and nuclear count was made on each patient about every 7 to 10 days. The laboratory data used for statistical study were (a) the white blood cell count, (b) the red blood cell count, and (c) the polymorphonuclear count.

The cases were divided into the following five groups according to the sex and type of arthritis: Group 1, males with rheumatoid arthritis; Group 2, females with rheumatoid arthritis; Group 3, males with miscellaneous arthritis; Group 4, females with miscellaneous arthritis; and Group 5, the 100 cases as a whole.

Frequency of the Development of Agranulocytosis in Patients Receiving Amidopyrin Medication. During the past 3 years, over

100,000 tablets of amidopyrin, or amidopyrin mixed with magnesium carbonate, were administered to 400 patients in the clinic and in private practice. Of these, 4 (1%) (1 male and 3 females) developed agranulocytosis and 3 of them died. Although this incidence is small, it is important because of the high mortality rate.

The male (aged 48) and 1 female (aged 33) had severe rheumatoid arthritis of long standing. The other females (aged 69 and 75) had osteoarthritis. Thus it appears that the agranulocytic syndrome usually occurs in elderly people or in those with long-standing infection. Therefore, amidopyrin is never given to patients over 60, or to those with long-standing infection, *e. g.*, rheumatoid arthritis with loss of weight, poor appetite, anemia, etc. Amidopyrin does not appear to affect the younger patients who do not have these complications.

TABLE 1.—ANALYSIS OF VARIATIONS IN THE 4 GROUPS.

Group.	Type.	No.	Cells.	P.E. of dif.	Dif.	%.	Result.
1	Males with rheumatoid arthritis	12	Lek.	±809.6	—557	0.690	Not significant.
			Polys.	±2.7031	—3	1.147	Not significant.
			R.B.C.	±123.690	+500,000	4.043	Significant (more than 3 X P.E.).
2	Females with rheumatoid arthritis	32	Lek.	±362.9	+1,028	2.800	Prob. significant.
			Polys.	±1.439	+1.	0.695	Not significant.
			R.B.C.	±69.935	+80,000	1.159	Not significant.
3	Males with miscellaneous arthritis	17	Lek.	±523.9	—107	0.200	Not significant.
			Polys.	±1.9587	+5	2.552	Doubt. significant.
			R.B.C.	±119.220	+160,000	1.342	Not significant.
4	Females with miscellaneous arthritis	39	Lek.	±325.5	+104	0.320	Not significant.
			Polys.	±1.2033	—3	2.552	Doubt. significant.
			R.B.C.	±73.783	+110,000	1.490	Not significant.
All cases		100	Lek.	±225	+290	1.289	Not significant.
			Polys.	±.8338	—158	.688	Not significant.
			R.B.C.	±44.559	+155,790	3.5	Significant.

In 5 other patients, the white blood cell count was reduced from about 5000 to about 3000 and the polymorphonuclear count was reduced from approximately 50 to 35%. On the other hand, an occasional initial polymorphonuclear count of about 35% was increased to about 55% with a coincident rise in the white blood cell count. Since a low white blood cell count and polymorphonuclear cell count existed in a few patients, the above-mentioned reductions in the white blood cell count were not considered significant.

Analysis of 100 Cases. (Exclusive of 4 that developed agranulocytosis.) The following standard formulas as published by Kent⁷ have been used in the calculations. Group 2 data are used for illustration.

Standard Deviation.

$$s = \sqrt{\frac{S(X^2)}{N}}, \text{ where } s = \text{standard deviation, } S = \text{the sum, } X^2 = \text{the}$$

squares of the individual deviations from the mean, and N = the number of values in the series, or:

$$s = \sqrt{\frac{\text{sum of the squares of the individual deviations from the mean}}{\text{number of cases}}}$$

If x = the initial determinations and y = the final determinations, then substituting the values of the white blood cell counts in Group 2, we have:

$S_x = \sqrt{\frac{107,616,900}{32}} = \sqrt{3,363,028} = \pm 1833.8$, which is the standard deviation of the initial white blood cell counts.

Likewise, $S_y = \sqrt{\frac{169,826,000}{32}} = \sqrt{5,307,060} = \pm 2303.8$, which is the standard deviation of the final white blood cell counts.

Probable Error of the Mean. Using the above symbols, the probable error of the mean (PE_m) is calculated as follows: $PE_m = 0.6745 \times \frac{S}{\sqrt{N}}$.

Substituting the values of the white blood cell counts, $PE_{mx} = 0.6745 \times \frac{1833.8}{\sqrt{32}} = \pm 218$, which is the probable error of the mean of the initial white

blood cell counts. Likewise, $PE_{my} = 0.6745 \times \frac{2303.8}{\sqrt{32}} = \pm 274$, which is the probable error of the mean of the final white blood cell counts.

Probable Error of the Difference. Pearl⁸ states that "The probable error of the difference between any two independent quantities (i. e., quantities such that there is no correlation between their errors) is equal to the square root of the sum of the squares of the probable errors of the quantities entering into the difference," or: $\sqrt{(PE_m X)^2 + (PE_m Y)^2}$ = the probable error of the difference, where X and Y are the independent quantities entering into the difference. In the present instance X = the initial and Y the final white blood cell counts. Substituting the values of the white blood cell counts: $\sqrt{(218)^2 + (274)^2} = \pm 362.9$, which is the probable error of the difference. According to Pearl,⁸ "It has been practically a universal custom among biometric workers to say that a difference (or a constant) which is smaller than twice its probable error is probably not significant, whereas a difference (or a constant) which is three or more times its probable error is either 'certainly' or 'almost certainly' significant." The difference equals the difference between the initial mean white blood cell count and the final mean white blood cell count, or $+1028$. Therefore, $\frac{1028}{362.9} = 2.8$, or the difference is over twice the probable error of the difference. Although this difference is slightly less than 3, the value, Pearl⁸ says, is certainly significant; it so closely approximates this number that it might be considered a significant increase.

The above methods of calculation are used throughout this analysis.

Discussion. When the series of 100 cases is considered as a whole, the only change noted is a significant increase in the red blood cell counts. When, however, the groups are analyzed separately, there is a definitely significant increase in the red blood cell counts in males with rheumatoid arthritis, a significant increase in the white blood cell counts of the females with rheumatoid arthritis and a possible significant decrease in the polymorphonuclear counts in females with miscellaneous arthritis. It is interesting to note that the red blood cell counts are increased in all groups and that no definitely significant hematologic decrease occurred in any group. From this, it might be maintained that agranulocytosis developing during the course of amidopyrin medication must be due to an individual hypersensitivity or idiosyncrasy.

Conclusions. Exclusive of 4 patients who developed agranulocytosis, there was no appreciable change in the white blood cell counts or polymorphonuclear counts of 100 patients who were given amidopyrin daily for prolonged periods.

There was a significant increase in the red blood cells.

Agranulocytosis developed in 1% of 400 patients who were given amidopyrin medication.

It is concluded that amidopyrin does not produce hematologic changes, except in certain isolated cases where there is probably an idiosyncrasy toward the drug.

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THE RELATION BETWEEN THE SUSPENSION STABILITY OF ERYTHROCYTES AND VARIOUS CONSTITUENTS OF PATHOLOGIC HUMAN BLOOD.*

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IN health the suspension stability of the blood is maintained with remarkable constancy. In disease it is diminished so that the erythrocytes separate from the plasma with varying degrees of rapidity. What is the cause of the increased rate of erythrocyte sedimentation?

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Fahraeus¹ concluded that the increased sinking velocity of the red blood corpuscles depends upon: (1) An increased agglutination of the corpuscles, and (2) on a diminution in their number. In a series of experiments in which he used horse blood proteins he showed that the "agglutination capacity of the plasma" was the primary factor in producing a rapid sedimentation of erythrocytes. He also showed that the most rapid sedimentation and, therefore, the maximum agglutination, took place in solutions of fibrinogen, the less rapid in solutions of globulin, and the least rapid in solutions of albumin. He further showed that there was no relation between the sedimentation rate and the total plasma proteins. In a second publication² he stated that the phenomena of increased sinking velocity of the red blood corpuscles and the increased percentage of serum globulin and fibrinogen occurring coincidentally, "stand in direct causality."

Westergren^{3,4} concluded that there was a definite correlation between the plasma or serum proteins and the rate of sedimentation of erythrocytes. *This rate is defined in millimeters of drop per hour of time.* From a series of 100 analyses, Westergren selected the middle 62 for statistical study. When he plotted the values for the various blood proteins against the sedimentation rate these appeared to fall along a straight line. Westergren's values for the correlation coefficients between fibrin, globulin, albumin and the sedimentation rate are shown in Table 1, p. 181.

Since Westergren's original data were published it has been considered advisable to subject them in their entirety to statistical analysis. The data were complete in 97 instances. Correlation coefficients, correlation ratios and partial correlations were calculated.* The results are shown in Table 2, p. 181.

* The correlation coefficient used in this study is that of Karl Pearson, $r_{xy} = \frac{\sum xy}{n\sigma_x\sigma_y}$. (Yule, G. U.: *An Introduction to the Theory of Statistics*, 10th ed., London, Charles Griffin & Co., p. 173, 1928.) It measures agreement or disagreement between two variables in terms of variations from their respective means. *It does not measure cause and effect*, although this conclusion may be reached by the investigator in the interpretation of his results.

The correlation ratios, $\eta_{xy} = \frac{\sigma_{mx}}{\sigma_x}$, $\eta_{yx} = \frac{\sigma_{my}}{\sigma_y}$ (Ibid., p. 205), measure the approach of values of x associated with given values of y (or *vice versa*) to a single-valued relationship of any form, not necessarily linear as is the case of the Pearson correlation coefficient. The difference between $\eta_{xy}^2 - r_{xy}^2$ is a measure of the divergence from linearity of the regression of x on y .

The partial correlation coefficient is used when three or more variables have been intercorrelated, using $r_{xy} = \frac{\sum xy}{n\sigma_x\sigma_y}$, and when one or more of these variables is held constant in order to determine their influence on the relationships established. If there were three variables, x , y and z , and it was desired to test the influence exerted by z on r_{xy} , z could be rendered constant by using the following formula for partial

correlation, $r_{xy.z} = \frac{r_{xy} - r_{xz} \cdot r_{yz}}{\sqrt{1 - r_{xz}^2} \sqrt{1 - r_{yz}^2}}$ (Ibid., p. 239.)

TABLE 1.—CORRELATION COEFFICIENTS BETWEEN SEDIMENTATION RATE, FIBRIN, GLOBULIN, ALBUMIN AND TOTAL PROTEIN. (COMPILED FROM WESTERGREN.)

r_{SR-F}	$= +0.82$	r_{SR-TP}	$= +0.15 \pm 0.12$
r_{SR-F^*}	$= +0.85$	r_{F-G}	$= +0.34$
r_{SR-G}	$= +0.50$	r_{F-A}	$= -0.30$
r_{SR-A}	$= -0.46$	r_{G-A}	$= -0.42$
r_{SR-FGA}	$= +0.87$		

* $n = 97$, all others $n = 62$. SR = sedimentation rate. F = fibrin. G = globulin. A = albumin. TP = total protein.

TABLE 2.—MEASURES OF RELATIONSHIP BETWEEN SEDIMENTATION RATE, FIBRIN, GLOBULIN AND ALBUMIN. (CALCULATED FROM WESTERGREN'S DATA.)

	Correlation coefficient.	Correlation ratios.	
		η_{xy} .	η_{yx} .
SR-F	+0.85	0.87	0.89
SR-G	+0.60	0.64	0.64
SR-A	-0.50	0.58	0.64
F-G	+0.54	0.56	0.58
F-A	-0.43	0.54	0.46
G-A	-0.56	0.57	0.62

TABLE 3.—COEFFICIENTS OF PARTIAL CORRELATION BETWEEN SEDIMENTATION RATE AND FIBRIN, GLOBULIN AND ALBUMIN. (CALCULATED FROM WESTERGREN'S DATA.)*

Zero order correlation coefficients.	First order partial correlation coefficients.	Second order partial correlation coefficients.
$r_{SRF} = +0.85$	$r_{SRF \cdot G} = +0.78$	$r_{SRF \cdot GA} = +0.77$
	$r_{SRF \cdot A} = +0.81$	
$r_{SRG} = +0.60$	$r_{SRG \cdot F} = +0.34$	$r_{SRG \cdot FA} = +0.26$
	$r_{SRG \cdot A} = +0.46$	
$r_{SRA} = -0.50$	$r_{SRA \cdot F} = -0.30$	$r_{SRA \cdot FG} = -0.18$
	$r_{SRA \cdot G} = -0.24$	

* All coefficients are significant in terms of their probable errors, except $r_{SRA \cdot FG}$.

The data in Tables 2 and 3 show:

1. The values of the correlation coefficients between sedimentation rate and fibrin, globulin and albumin, respectively, when the total number of cases is studied, agree with Westergren's findings as published for the selected sample.

2. By calculating correlation ratios it was found that these are not significantly higher than the correlation coefficients. It may be assumed, therefore, that the relationships between sedimentation rate and the various serum proteins are linear.

3. By calculating the partial correlations upon which the multiple coefficient ($r_{SR \cdot FGA}$) depends, it was found that the increase in sedimentation rate and the increase in the amount of fibrin are closely related even when globulin and albumin are rendered constant, but that an increase in globulin is not correlated to any appreciable extent with rapidity of sedimentation after the influence of fibrin is rendered constant. The negative correlation between sedimentation rate and albumin (-0.50) seems to depend entirely upon the *negative* relationship between albumin and fibrin

and albumin and globulin, because, when fibrin and globulin are rendered constant the correlation is reduced almost to zero.

4. These findings explain the high multiple correlation coefficient (0.87) which Westergren obtained between sedimentation rate and fibrin, globulin and albumin when taken collectively. The increase in the multiple correlation coefficient of only 0.05 over the highest zero order correlation coefficient (0.82 between sedimentation rate and fibrin, Table 1) indicates that the globulin and albumin play little, if any, part in establishing the positive multiple correlation. It must also be pointed out that the correlation coefficient between sedimentation rate and albumin is negative, as are also the correlations between fibrin and albumin, and globulin and albumin. The multiple correlation coefficient is always positive in sign and greater than the highest value of any correlation which is contained in its formula.

The following study was undertaken in order to determine what effects variations in the blood serum proteins and blood counts have upon the suspension stability of erythrocytes. The suspension stability is defined as those forces tending to impede the sedimentation of erythrocytes in plasma. *An increase in suspension stability indicates a prolongation in sedimentation time and vice versa.*

Materials and Methods. An attempt was made to obtain samples from hospital patients suffering from a variety of illnesses and exhibiting wide variations in sedimentation time. Samples from normal persons were excluded from this study.

With few exceptions all analyses were done on a single sample of venous blood. In most of the cases the blood counts were done on blood obtained from the finger or ear shortly before or immediately after collection of the sample of venous blood.

All of the sedimentation tests were done as follows: 0.2 cc. of 5% sodium citrate solution was aspirated into a tuberculin syringe, then 0.8 cc. of blood was aspirated and this mixture was thoroughly agitated. The sample of citrated blood, free of air bubbles, was transferred to a Friedlaender tube and the time necessary for the column of erythrocytes to settle 18 mm. was recorded.

The serum protein, globulin and albumin analyses were done by means of the clinical methods of Greenberg.⁵

The hemoglobin was determined by means of a Sahli hemoglobinometer (100% equals 14 gm. of hemoglobin per 100 cc. of blood), and the standard methods were employed for counting erythrocytes and leukocytes.

The data for sedimentation time, total protein, serum albumin, serum globulin, albumin-globulin ratio, red blood corpuscle count, hemoglobin content, white blood cell count and neutrophil count obtained from 102 patients suffering from various diseases were compiled and studied.

Globulin. The correlation coefficient of -0.27 between sedimen-

tation time and globulin content, although of low magnitude, is statistically significant. On the average, when the globulin content is low the sedimentation time is prolonged.

TABLE 4.—MEANS, STANDARD DEVIATIONS AND MEASURES OF RELATIONSHIP BETWEEN SEDIMENTATION TIME AND VARIOUS CONSTITUENTS OF PATHOLOGIC HUMAN BLOOD (102 CASES).*

	Means.	Standard deviations.	Correlation coefficients with sed. time.	Correlation ratios with sed. time.	
				η_{yST} .	η_{STy} .
Globulin	2.54	0.61	-0.27	0.33	0.31
Albumin	3.92	0.79	+0.23	0.28	0.27
A/G ratio	1.62	0.44	+0.43	0.50	0.47
Total protein	6.51	1.10	+0.06	0.24	0.27
R.B.C. count	4.25	0.80	+0.41	0.52	0.58
W.B.C. count	10,658	15,622	+0.26	0.91†	0.34
W.B.C. count†	10,015	5,845	+0.11	0.25	0.16
Pmn count	68.80	15.50	-0.28	0.55	0.44
Sedimentation time	96.00	117.50			
Sedimentation time†	92.50	112.00			

* All coefficients are significant in terms of their probable errors excepting +0.06, +0.11 and 0.16.

† Case No. 100 omitted (W.B.C. count, 160,000).

‡ This value for η of W.B.C./ST is disproportionately high because of the inadequate distribution which results when arrangements are made to accommodate Case No. 100.

Albumin. The correlation coefficient of +0.23 between sedimentation time and albumin is low but statistically significant. On the average, when the albumin content is high, the sedimentation time is prolonged. The positive correlation of 0.43 between the albumin-globulin ratio and the sedimentation time indicates that, on the average, as the sedimentation time becomes prolonged, the greater the content of albumin relative to globulin.

Total Protein. There is no linear relation between sedimentation time and total protein. The correlation ratios show a low statistically significant value along a curve. This probably depends upon the fact that as the value for the sedimentation time increases above the mean, the total protein, showing less variation, reaches a level around its mean. It must be pointed out that only 8 cases in a total of 102 functioned to produce this effect. It is also interesting that these same 8 cases have red blood corpuscle counts greater than the mean for red blood cell counts.

Red Blood Cell Count. The correlation coefficient of +0.41 signifies that, on the average, as the red blood corpuscle count increases, the sedimentation time also increases and *vice versa*.

White Blood Cell Count. The total white blood cell count bears little, if any, relationship to the sedimentation time. On the other hand, as the sedimentation time increases, the neutrophil count decreases and *vice versa*. This relationship fits a curve better than it does a straight line, as is indicated by the difference between the correlation coefficient of -0.28 and the η_{yST} of 0.55.

Discussion.—From the foregoing presentation of the data of Westergren (Table 3) it *appears* that the sedimentation rate is influenced to a certain degree by the fibrin content and to a much lesser degree by the globulin content of the plasma. To conclude that a cause and effect relationship exists between an increase in the globulins (fibrin and globulin) and an increase in the sedimentation rate is not justifiable. A cause and effect relationship cannot be inferred from our data.

TABLE 5.—VALUES FOR THE PLASMA PROTEINS AND SEDIMENTATION TIME OF THE BLOOD OF HORSES, RABBITS AND MAN.

	Total serum protein.	Albumin.	Globulin.	Fibrin.	Fibrinogen.	Sed. time, min.
Horse ⁶	6.95	2.46	3.84	0.65		
Horse ¹⁰	8.04	2.80	4.79	..	0.45	
Horse ⁷ :						
Age, 1-2.5 yrs.	6.21-7.40	2.22-2.84	3.38-5.22	15-60
Age, 4-15 yrs.	6.94-8.63	1.82-3.02	3.92-6.13	
Horse ⁵	5.76-7.23	3.01-3.27	2.49-4.17	..	0.34	
Man ⁸	7.19	4.45	2.73	..	0.30	
Man ¹⁰	7.26	4.01	2.83	..	0.42	180-660
Rabbit ⁸	5.55-6.05	4.10-4.47	1.45-1.58			
Rabbit ⁹	5.40	3.03	1.86	0.50	..	600-2400

A study of the variations in sedimentation time in relation to plasma and serum proteins in different species reveals that some factor other than the proteins must be responsible for altering the suspension stability of the blood. The blood serum globulin content among the different species does not vary to any great extent, while the sedimentation time which does, appears to be characteristic for each species. The values charted in Table 5 illustrate that the variations in sedimentation time are out of proportion to the variations in the different protein values.

TABLE 6.—VALUES FOR THE PLASMA PROTEINS AND SEDIMENTATION TIME OF THE BLOOD IN NEPHROSIS.

Case.	Total serum protein.	Serum albumin.	Serum globulin.	Sed. time, min.
1	2.76	0.95	1.51	7
2	2.80	1.00	1.80	8
3	3.85	2.40	1.45	16
4	5.48	2.17	3.31	17
5	3.90	2.01	1.70	18
6	4.74	2.20	2.54	30
7	6.30	3.26	3.03	30
8	4.39	2.96	1.55	52

A similar phenomenon may be observed if one studies the variations in the protein and sedimentation time in a series of cases of nephrosis. Here again it is noted that the variations in the sedimentation time is great, while the variation in the globulin content is much less. In addition, the prolongation of the sedimentation time does not parallel the values found for serum globulin.

Fahraeus¹ pointed out that the red blood corpuscles are agglutinated by many substances, including certain colloids and emulsoids and that the rapidity of formation and size of the agglutinated mass of corpuscles bears a certain relationship to the rate of sedimentation.

Lucia and Brown¹¹ have shown that the suspension stability of erythrocytes is markedly diminished in solutions of gum acacia *in vivo* and *in vitro*. They state that, "although there appears to be an association between an increase in blood serum globulins and a diminished suspension stability, the real causative factor is an agglutinant which may or may not be associated with the globulins."

In another series of *in vitro* experiments it was shown that the suspension stability of erythrocytes was more often increased than decreased in solutions of animal and human blood serum globulins.¹²

Summary. An analysis of the suspension stability of erythrocytes in 102 cases reveals that the sedimentation time is apparently accelerated as the globulin content of the serum increases and is retarded as the albumin content of the serum increases. These correlations, although low in value, are statistically significant. A cause and effect relationship cannot be said to exist between an increase in the blood serum globulin and an acceleration in the sedimentation time.

A diminution in the red blood corpuscle count, or an increase in the neutrophil count, is associated with an increase in the sedimentation time.

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THE RELATIONSHIP BETWEEN ALCOHOLIC INTOXICATION
AND ANOXEMIA.*

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FREQUENT references have been made in studies of anoxemia, on mountain expeditions, altitude flights or in low oxygen chambers, to the similarities in the behavior of a person suffering from oxygen want to one under the influence of alcohol. Barcroft¹ believes that the symptoms of acute anoxia are precisely those of alcoholic intoxication and that "acute oxygen want simulates drunkenness, while chronic anoxemia simulates fatigue." Under both conditions a person may become irrational and uninhibited and lose the capacity for self-criticism, association, memory, sensitivity and motor control. In summarizing the psychological effects of anoxemia McFarland² has also pointed out this striking resemblance and in experiments with low oxygen he reported that the most frequent initial remark from naive observers was related to feelings of alcoholic intoxication.

After Y. Henderson³ discovered that CO₂ caused a more rapid de-etherization after narcosis, Hunter and Mudd⁴ reported that patients in coma due to alcohol were improved in some cases to the state of mental clarity following the inhalation of 7 to 10% CO₂ for one-half hour. Palthe⁵ found in guinea pigs and rabbits that the loss of control of postural reflexes due to alcohol could be improved by inhaling pure oxygen. In human subjects he observed that acute symptoms of intoxication following excess alcohol could be counteracted with pure oxygen and that delirium tremens patients could be improved with oxygen (with or without 5% CO₂). Recently Robinson and Selesniek⁶ reported striking reduction in the venous blood alcohol of inebriates following the inhalation of 90% O₂ and 10% CO₂ for $\frac{1}{2}$ hour. Newman and Card⁷ found no significant change however in the total body alcohol of less intoxicated subjects under similar experimental conditions.

Hunter and Mudd attributed the more rapid elimination of alcohol to the increased pulmonary ventilation induced by the CO₂ while Palthe thought the oxygen counteracted the reduced oxygen metabolism of tissue cells produced by the alcohol since the symptoms reappeared if the oxygen mask was removed too soon. Thus it appears that oxygen and CO₂ tend to reduce the symptoms of alco-

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holism. But it is not clear whether this effect is due to a diminution of alcohol in the blood or to a facilitation of the use of oxygen in the tissues.

Himwich⁸ has reviewed the evidence relative to elimination of alcohol from the body and to the variables which influence the rate of oxidation. Mellanby⁸ says that alcohol is oxidized at a constant rate regardless of the amount present in the body. Haggard and Greenberg⁹ take exception to Mellanby's view however, stating that the rate of oxidation is proportional to the amount present. Only a small proportion is eliminated through the lungs, kidneys and skin. For the most part alcohol disappears from the blood after absorption by oxidation in the tissues and supplies a limited amount of energy. Durig¹⁰ found the use of alcohol as a source of muscular energy physiologically unsound in mountain climbing at high altitudes. This finding is in agreement with the observation of Himwich,¹¹ of an increase in lactic acid following the ingestion of alcohol. According to Carpenter^{12,13} the disappearance of alcohol is accounted for in terms of heat and not in energy for bodily use. Contrary to the findings of Voltz and Baudrexel,¹⁴ Carpenter reported that the amount of work in exercise experiments had no significant effect on the rate of oxidation as determined by the respiratory exchange and the amount of alcohol in the expired air, urine and blood. In testing the response of subjects to a standard exercise in air and in high percentages of oxygen with and without alcohol, Barach¹⁵ found that breathing 50% O₂ produced a greater percentage decline in rate of respiration and pulmonary ventilation in exercising subjects who had ingested alcohol than in those who had not.

In following the course of alcohol in the blood of rabbits at sea level and at high altitudes Biehler¹⁶ reported that the concentration decreased with increasing altitude. He attributed this effect to the greater frequency of breathing at high altitudes. Bornstein and Loewy¹⁷ attribute Biehler's results to the fact that the rabbits were not tested under fasting conditions. They found, on the contrary, that the concentration of alcohol in the blood of fasting human subjects rose more rapidly and to a higher level at high altitudes than at sea level. The R. Q. also fell more after the ingestion of alcohol at high altitude than at sea level. McFarland and Forbes¹⁸ in a recent study in the Andes at 17,500 feet confirmed these results. Thus alcohol appears to have greater effect at high altitudes and this may be related to the anoxemia known to exist under these conditions.

Gettler¹⁹ believes that the lower concentration of alcohol one finds in the blood of the habitual drinker as compared to the neophyte is due to increased capacity for oxidation. In experiments with dogs he observed that the ingestion of increasingly greater amounts of alcohol was followed by increased tolerance to theoretically lethal doses.

Various theories have been proposed to account for the symptoms which follow the ingestion of alcohol with general agreement that it is a depressant. Verworn²⁰ believed that the essential means by which a narcotic acted was through the medium of suppressed oxidation. Warburg²¹ has shown that alcohol diminishes the O₂ combining power of red blood corpuscles. Keilin²² found that alcohol did not prevent the oxygenation of cytochrome (respiratory pigment) in tissue cells, but that it did appear to stabilize the oxytochrome so that the oxygen could not be removed with normal ease. Quastel²³ believes that all narcotics including alcohol inhibit the oxidation of substances important in carbohydrate metabolism in the brain tissue, viz., glucose, lactic acid and pyruvic acid. Since one of the chief sources of energy of the brain lies in the oxidation of lactic acid, alcohol, according to Quastel, will diminish the supply of energy and hence depress functional activity. In studies of excised brain tissue Robertson and Stewart²⁴ have shown that alcohol depresses the rate of oxidation by a high degree of absorption on the colloidal surfaces of the oxidative enzyme areas of the brain cells and displaces the more usual metabolites. Since there is no deficit of oxygen in the blood except under conditions of severe shock, the symptoms can be attributed to the inability of the cells to utilize the oxygen in the blood. Such studies led Peters and Van Slyke²⁵ to classify acute alcoholism as a histotoxic anoxia.

It appears that alcohol is ultimately a depressant and that the effect is related to the impairment of oxidation in the tissues, especially the nervous tissue. It has been demonstrated that excess oxygen and carbon dioxid will improve the well-being and mental clarity of a person suffering from excess alcohol. It is not clear, however, whether the excess oxygen acts by way of the tissues or by lowering the concentration of alcohol and lactic acid in the blood. The present investigation, therefore, has been carried out to determine the extent to which alcohol brings about a condition of anoxia and the extent to which the inhalation of 50 to 60% oxygen and from 0.2 to 10% carbon dioxid will counteract the effects of excess alcohol. The criteria used were: 1, blood lactic acid; 2, blood alcohol and 3, reactions to psychological tests.

Experimental Procedure. The subjects were tested in a Barach portable oxygen chamber, 7 feet high by 8 feet square, where the percentage of oxygen and carbon dioxid, the temperature, and ventilation could be regulated. The ventilation was provided by a motor blower which circulated the air through a tank containing large chunks of ice to cool and dry the air. The temperature was maintained between 65° and 70° F.; the humidity between 40 and 50%. The oxygen and carbon dioxid concentrations were maintained at the desired percentages by running in gas from cylinders outside the chamber. Determinations were made every 15 minutes on a simplified Haldane gas analysis apparatus.

Twenty-three non-drinking, with the exceptions of Mos and Boo, students served as subjects. The average age was 23 years and the average weight

75 kilos. Each subject was given a series of physical efficiency tests including basal metabolism and the Schneider index of neurocirculatory failure. Four of the subjects (Fre, Sor, Wal and Art) had basal rates below -18. All were found to be in good physical condition.

The subjects came to the laboratory in the morning without breakfast. After resting on a bed for 30 minutes they entered the chamber and were given the drink. In the lactic acid series under strictly basal conditions the subjects spent the night near the laboratory and reclined on a bed inside the chamber throughout the experiment. The subjects were unaware of the changes in the oxygen content except in the 5% carbon dioxid series which caused some distress because of the increased rate of respiration.

The alcohol was ingested in doses of approximately 1 gm. per kilo of body weight and diluted in proportions of $\frac{1}{3}$ alcohol to $\frac{2}{3}$ water and orange juice. An attempt was made to disguise the alcohol with oil of orange and oil of juniper. This was difficult since the subjects could frequently detect the alcohol drinks from the controls due to the sensations in the intestinal tract.

Samples of venous blood were taken $\frac{1}{2}$, 1 and 2 hours after the ingestion of the alcohol. In the lactic acid series a control sample was taken before the alcohol drink and care was taken to keep the subject from getting excited or from muscularly exerting himself. Twenty cc. of blood was drawn each time for the alcohol determinations, and 20 cc. for the lactic acid. Duplicates were run in each case. The amount of alcohol in the blood previous to the ingestion of alcohol with this method averages 0.012 gm. per cc. In 5 of our subjects the range was .011 to .014 mg. per cc. (Table 5). Gettler's method¹⁹ was used in determining the blood alcohol and the Freidemann, Cotonio and Shaffer²⁰ method for lactic acid. The error of the Gettler method is 3 to 5% and the lactic acid method 3%.

Six psychological tests of varying degrees of complexity were given following the ingestion of alcohol to 14 subjects in the following order: 1, Choice Reaction, 2, Digit Symbol, 3, Color Naming, 4, Pursuit Meter, 5, Code Transliteration, and 6, McDougall Dotting test. The Choice Reaction test involved reacting as quickly as possible to one of 5 colored lights by pressing the corresponding key—score in hundredths of a second. In the Digit Symbol test the subject learned a code and wrote down the numbers corresponding to the symbols—score total number of digits transliterated in 4 minutes. The Color Naming test involved repeating as rapidly as possible the names of 400 colors consisting of 5 different colors—score in seconds. The Pursuit Meter involved keeping two pointers directly opposite each other, one pointer being controlled by an irregular cam. The deviations were recorded automatically—score total amount of deviation. The Code test required the subject to transliterate 50 letters as rapidly as possible—score in seconds. The McDougall Dotting test required the subject to mark the middle one of three dots in a row haphazardly spaced and exposed momentarily on a rotating drum—score total number of dots touched.

The respiratory rate, pulse rate and blood pressure were taken at the beginning and end of each experiment except in Part III where the pulse rate was taken every 15 minutes throughout the 2 hours.

PART I. In the first experiment 4 subjects, Wes, Edw, Mos, and Rob, were given the various psychological and physiological tests discussed above after the ingestion of $\frac{3}{4}$, 1 and $1\frac{1}{4}$ gm. of ethyl alcohol per kilo of body weight, approximately 60 cc., 80 cc., and 100 cc. The subjects took the psychological tests while seated at a table in the chamber.

Table 1 and Figure 1 shows the percentage of alcohol in the blood of subjects breathing air and 50% oxygen and 2% carbon dioxide following the ingestion of various alcohol drinks. In comparing the amount of alcohol in the blood after the ingestion of $\frac{3}{4}$ gm. per kilo

A BLOOD ALCOHOL (gm. per 100 cc.). B

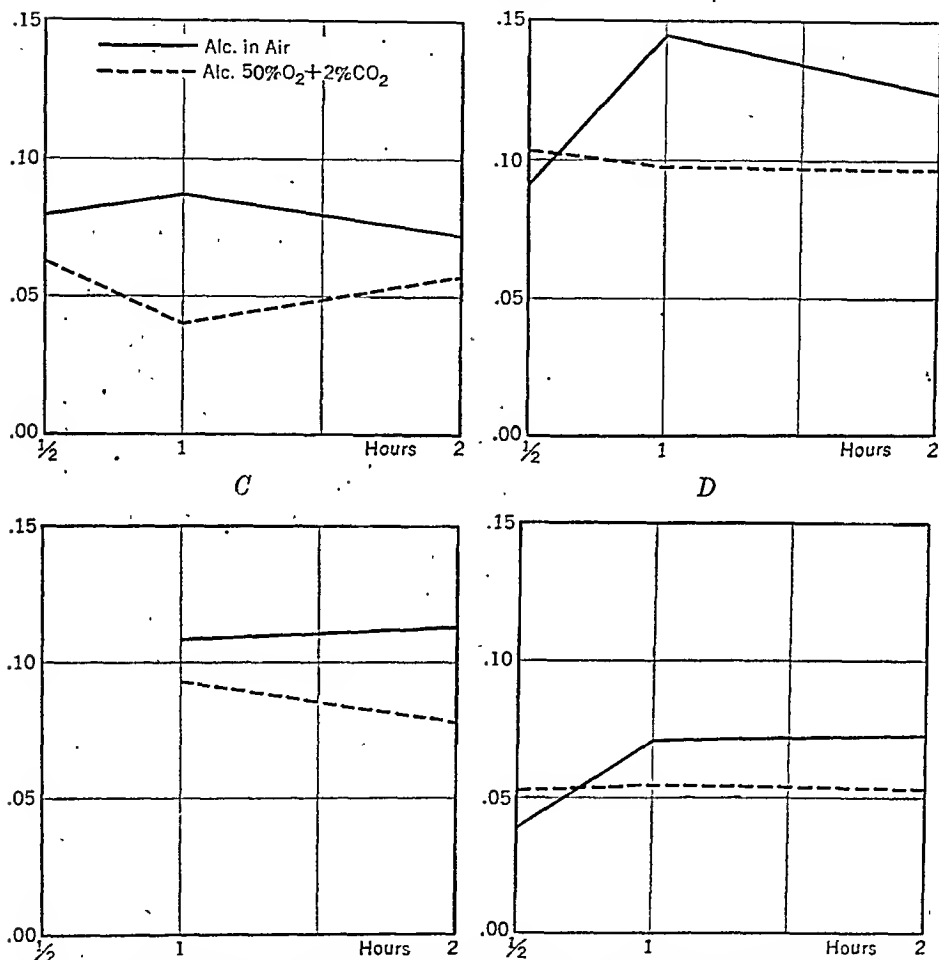
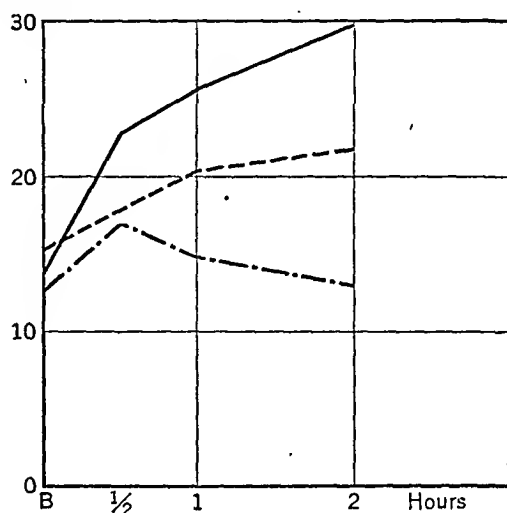
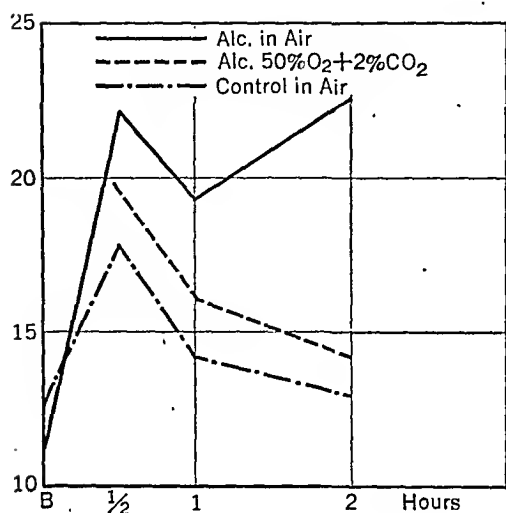


FIG. 1.—Grams of alcohol per 100 cc. of blood following ingestion of alcohol. A, $\frac{3}{4}$ gm. per kilo body weight—curves based on averages of 13 subjects; B, 1 gm. per kilo body weight—4 subjects; C, $1\frac{1}{4}$ gm. per kilo body weight—4 subjects; D, $\frac{3}{4}$ gm. per kilo body weight—10 subjects. Basal conditions maintained throughout blood sampling period.

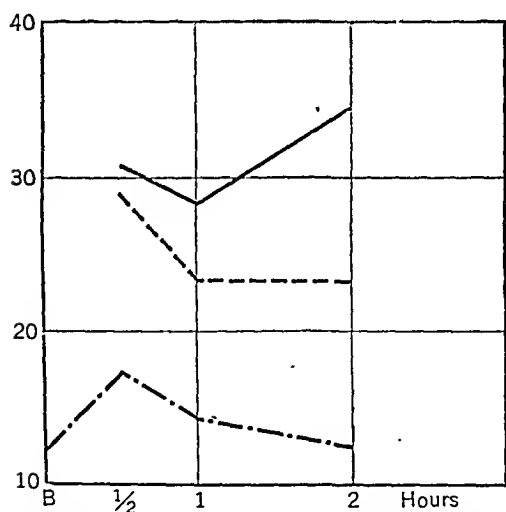
body weight in air with a similar drink in 50% oxygen and 2% carbon dioxide two subjects, Wes and Mos, were not affected and 2 subjects, Edw and Rob, were benefited by the oxygen-carbon dioxide mixture. In the second series with 1 gm. per kilo body weight in high oxygen the blood alcohol determinations were lower in all 4 of the subjects. With the largest drink of alcohol, i. e., $1\frac{1}{4}$ gm. per

kilo body weight, the improvement was very significant after 1 hour in the cases of Wes, Rob, and Mos. In this series the procedure was slightly altered in that each subject breathed mixtures of 80% oxygen and 10% carbon dioxid through a mask for 15 minutes

A LACTIC ACID (mg. per 100 cc.). B



C



D

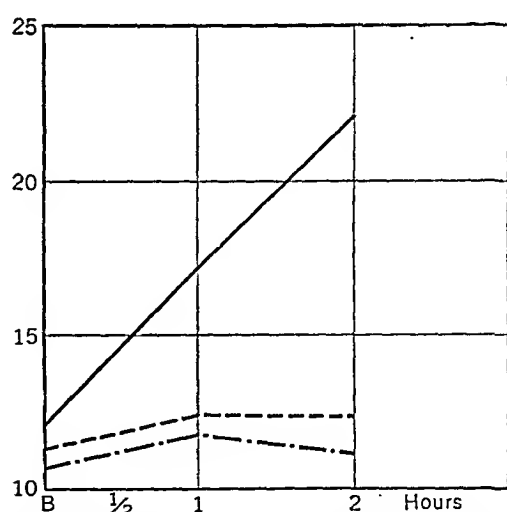


FIG. 2.—Milligrams of lactic acid per 100 cc. of blood following ingestion of alcohol. A, 1/4 gm. per kilo body weight—curves based on averages of 4 subjects. The alcohol-air curve is based on 9 subjects; B, 1 gm. per kilo body weight—4 subjects; C, 1 1/2 gm. per kilo body weight—4 subjects; D, 1/4 gm. per kilo body weight—5 subjects. Basal conditions maintained throughout blood sampling period.

following the ingestion of the alcohol and previous to entering the chamber. The differences are statistically reliable in the 1 gm. and 1 1/2 gm. per kilo body weight-series in 50% oxygen and 2% CO₂ as compared to air.

Table 2 and Fig. 2 show the milligrams of lactic acid per 100 cc. of blood just before the drink was taken and 1/2, 1 and 2 hours follow-

ing the ingestion of the various alcohol drinks as indicated. The increase in lactic acid following the control drink (no alcohol) was negligible. In the 10% oxygen (control drink with no alcohol) as well as following the ingestion of alcohol in air, there were significant increases in the lactic acid. These results are in accord with Himwich,¹¹ who states that the lactic acid concentration in the blood of human subjects is increased after the ingestion of alcohol. On examination of Table 2 one finds in comparing the lactic acid determinations of subjects breathing high oxygen with the same subjects breathing normal air that the lactic acid is lower in 10 of 12 cases after 2 hours and in 4 of 8 cases after 1 hour.

TABLE 1.—BLOOD ALCOHOL DETERMINATION FOLLOWING THE INGESTION OF DILUTED ETHYL ALCOHOL IN AIR, AND IN 50% O₂ AND 2% CO₂.

Condition.	Period, hours.	Grams per 100 cc. of blood.			
		Wes	Edw	Mos	Rob
$\frac{3}{4}$ gm. alcohol in air	$\frac{1}{2}$.094	.089	.094	.110
	1	.089	.096	.098	.103
	2	.065	.083	.087	.095
$\frac{3}{4}$ gm. alcohol in 50% O ₂ and 2% CO ₂	$\frac{1}{2}$.089	.086	.096	.118
	1	.085	.080	.097	.091
	2	.065	.076	.085	.075
1 gm. alcohol in air	1	.084	.110	.102	.135
	2	.134	.126	.100	.091
1 gm. alcohol in 50% O ₂ and 2% CO ₂	1	.128	.093	.074	.079
	2	.103	.077	.062	.071
1 $\frac{1}{4}$ gm. alcohol in air	$\frac{1}{2}$.057	.064	.112	.134
	1	.076	.152	.211	.145
	2	.125	.107	.107	.156
1 $\frac{1}{2}$ gm. alcohol in 50% O ₂ and 2% CO ₂	$\frac{1}{2}$.058	.107	.113	.121
	1	.052	.093	.109	.107
	2	.050	.089	.121	.098

PART II. Because there was a certain amount of movement involved in taking the psychological tests, a second series of lactic acid determinations was made on 5 subjects, Wes, Mos, Wal, Kne, and Rob, under strictly basal conditions. They reclined on a bed for an hour outside the chamber and after taking the first sample of blood they entered the chamber and laid quietly on the bed for the 2-hour period. In each case a sample of blood (20 cc.) was taken before the control or the alcohol drink and also 1 hour and 2 hours later. The results are shown in Table 3 and Graph D of Fig. 2. In the control series (no alcohol) there was no significant increase in lactic acid during the 2-hour session. After the ingestion of $\frac{3}{4}$ gm. of ethyl alcohol per kilo of body weight, all 5 subjects tested in air showed an increase in lactic acid which was verified on 2 subjects, Wal and Kne, on a repeated test. Later the 5 subjects took a similar drink in the chamber filled with 50% oxygen—2% carbon dioxide. Basal conditions were maintained throughout the experiment. With the exception of Kne there was a slight increase in each case, but

significantly less than in air. The series was repeated on Wal and Kne as in the previous series in alcohol and air and the results were verified. The average lactic acid determination was significantly greater for all 5 subjects while breathing air compared with 50% oxygen and 2% carbon dioxid. That is, the chances were 98 to 99 in 100 that the differences were reliable.

TABLE 2.—LACTIC ACID DETERMINATIONS AFTER THE INGESTION OF DILUTED ETHYL ALCOHOL IN AIR, AND IN 50% O₂ AND 2% CO₂.

Condition.	Period, hours.	Milligrams per 100 cc. of blood.			
		Rob	Edw	Mos	Wes
Control drink in air	B	16.6	15.3	16.5	12.1
	1	17.2	17.5	21.9	12.6
	2	15.4	16.0	18.3	9.7
Control drink 10% O ₂	B	17.3	13.4
	$\frac{1}{2}$	35.2	27.3	
	1	21.6	36.3	25.9	34.4
	2	24.3	39.9	30.8	46.9
$\frac{3}{4}$ gm. alcohol in air	B	14.3	10.2	9.7
	$\frac{1}{2}$	22.6	12.6	9.4
	1	30.1			
	2	24.9	19.2	18.3	29.9
$\frac{3}{4}$ gm. alcohol in 50% O ₂ and 2% CO ₂ .	$\frac{1}{2}$	20.4	17.9	17.4	22.4
	1	19.2	14.4	14.6	
	2	15.3	13.4	16.1	12.1
1 gm. alcohol in air	B	10.4	16.7
	$\frac{1}{2}$	23.3	26.7		
	1	26.7	35.3	23.8	16.8
	2	28.6	34.2	26.5	28.5
1 gm. alcohol in 50% O ₂ and 2% CO ₂ .	B	14.2	16.2	12.1	17.5
	1	21.9	23.0	28.7	19.0
	2	28.1	19.0	18.3	20.6
1 $\frac{1}{4}$ gm. alcohol in air	$\frac{1}{2}$	26.4	41.8	26.7	28.9
	1	22.2	43.4	24.2	22.8
	2	31.0	40.9	42.3	24.6
1 $\frac{1}{4}$ gm. alcohol in 50% O ₂ and 2% CO ₂	$\frac{1}{2}$	30.7	35.1	24.0	26.2
	1	21.8	23.7	24.2	23.5
	2	24.6	20.7	23.1	24.7

PART III. In this part of the experiment 5 subjects, Wol, Mel, Fre, Ber, and Joh, were given the series of psychologic and physiologic tests after the ingestion of $\frac{3}{4}$ gm. of alcohol per kilo body weight. Blood samples were drawn $\frac{1}{2}$, 1, and 2 hours following the ingestion of the alcohol.

In order to control the practice effects in the psychologic tests and also to check each blood alcohol series under similar conditions, each subject came without breakfast to the laboratory 11 times during a 3-month period. The experiments were given in the following order:

1. Control drink—air.
2. Control drink—50% oxygen.

3. Alcohol—50% oxygen and 2% carbon dioxid.
4. Alcohol—air.
5. Alcohol—50% oxygen plus 5% carbon dioxid.
6. Alcohol—50% oxygen plus 5% carbon dioxid.
7. Alcohol—air.
8. Alcohol—50% oxygen plus 2% carbon dioxid.
9. Alcohol—50% oxygen plus 0.2% carbon dioxid.
10. Control drink—50% oxygen.
11. Control drink—air.

TABLE 3.—LACTIC ACID DETERMINATIONS UNDER STRICTLY BASAL CONDITIONS FOLLOWING THE INGESTION OF DILUTED ETHYL ALCOHOL IN AMOUNTS EQUAL TO $\frac{1}{2}$ GM. PER KILO BODY WEIGHT.

Condition.	Period, hours.	Milligrams per 100 cc. of blood.				
		Wes	Mos	Wal	Kne	Rob
Control drink in air . . .	B	8.2	9.5	16.2	10.4	9.6
	$\frac{1}{2}$	18.0		
	1	10.0	10.0	17.6	11.3	10.4
	2	8.9	9.2	15.6	10.7	11.3
Alcohol in air: I . . .	B	9.3	9.7	15.0	17.1	10.1
	$\frac{1}{2}$	21.8	
	1	16.8	12.3	23.8	21.8	11.8
	2	22.9	17.3	26.0	24.4	20.0
Alcohol in air: II . . .	B	16.7	12.8	
	1	22.5	15.7	
	2	20.6	15.5	
Alcohol, 50% O ₂ and 2% CO ₂ : I . . .	B				A	B
	1	8.6	9.2	14.1	16.7	17.5
	2	11.3	11.5	12.3	16.5	22.0
	2	11.5	12.0	13.1	14.6	18.8
Alcohol, 50% O ₂ and 2% CO ₂ : II . . .	B					
	1	14.9	9.8	
	2	19.6	9.6	
	2	18.4	8.1	

Table 4 and Fig. 1 shows the grams of alcohol per 100 cc. of blood under the various conditions as indicated. If one compares the concentration of alcohol in the blood while breathing air with the series while breathing concentrations of 50% oxygen plus 0.2 to 5% carbon dioxid, it is apparent that the oxygen and carbon dioxid had the effect of lowering the alcohol concentrations. These differences are statistically significant.

After the ingestion of alcohol in air there was an initial increase in the pulse rate followed by a fall. If a similar alcohol drink was taken while breathing concentrations of 50% oxygen and 5% carbon dioxid, then there was a noticeable increase in the pulse rate as well as in the variability which was associated with the increased pulmonary ventilation due to the excess carbon dioxid. If the alcohol was taken while breathing 50% oxygen and 2% carbon dioxid, the rate and variability of the pulse was diminished as compared to a similar alcohol drink in air. There was a tendency

for the pulse rate to be slowed in the control series with no alcohol and 50% oxygen in the inspired air.

TABLE 4.—BLOOD ALCOHOL DETERMINATIONS FOLLOWING THE INGESTION OF DILUTED ETHYL ALCOHOL IN AMOUNTS EQUAL TO $\frac{3}{4}$ GM. PER KILO BODY WEIGHT.

Condition.	Period. hours.	Grams per 100 cc. of blood.				
		Wol	Mel	Fre	Ber	John
Alcohol in air: I	$\frac{1}{2}$.056	.066	.131	.084	.114
	1	.109	.190	.104	.084	
	2	.090	.102	.177	.069	.065
Alcohol in 50% O ₂ and 2% CO ₂ : I	$\frac{1}{2}$.043	.018	.043	.032	.059
	1	.048	.017	.058	.054	.052
	2	.058	.035	.052	.051	.040
Alcohol in 50% and 5% CO ₂ . .	$\frac{1}{2}$.073	.030	.085	.046	.068
	1	.101	.048	.083	.058	
	2	.108	.063	.077	.079	.069
Alcohol in 50% and 5% CO ₂ : II	1	.054	.121	.089	.068	
	2	.089	.106	.074	.082	
Alcohol in air: II	$\frac{1}{2}$068			
	1	.058	.084	.082	.059	
	2	.102	.092	.164	.082	
Alcohol in 50% O ₂ and 2% CO ₂ : II	1	.085	.118	.087	.094	
	2	.080	.090	.094	.095	
Alcohol in 50% O ₂ and 0.2% CO ₂ : I	$\frac{1}{2}$.090	.050	.092	.074	.060
	1	.099	.059	.090	.073	.065
	2	.100	.059	.061	.050	.059

PART IV. Fourteen subjects were given an alcohol drink corresponding to $\frac{3}{4}$ gm. per kilo body weight diluted with water and orange juice to equal a total volume of approximately 250 cc. Each subject came to the laboratory twice and was tested once in air and once on 50% oxygen and 2% carbon dioxid. Twenty cc. of venous blood was taken $\frac{1}{2}$, 1, and 2 hours after the ingestion of the alcohol. The results are given in Table 5. The procedure was slightly different in the case of Kne, Sor, Eck and Fel in that they took the series of psychologic tests mentioned above. All of the other subjects reclined on the bed throughout the 2-hour period. The averages of the blood alcohol determinations in air as compared with high oxygen gave statistically reliable differences for this group of 14 subjects. The differences were not reliable for individuals Eck, Sch, Cum, Dem, and Har. In the case of Sor, Wal and Art whose basal rates were below -20 the differences were very marked.

In order to determine the effects of 50% oxygen plus 2% carbon dioxid as compared to air, on the concentration of alcohol in the blood, the average for 23 subjects for the alcohol drink consisting of $\frac{3}{4}$ gm. per kilo body weight was computed. The averages for 50% oxygen and air were compared at $\frac{1}{2}$, 1, and 2 hours and treated by Fisher's method²⁷ for the reliability of the observed difference. The results indicate that $\frac{1}{2}$ hour after the ingestion

of alcohol the chances are 70 to 80 in 100 that the observed difference is reliable, *i. e.*, that the excess oxygen had a beneficial effect. At the end of the 1-hour and 2-hour periods, the chances are 99 in 100 that the decrease in blood alcohol in the high oxygen and carbon dioxid is reliable.

TABLE 5.—BLOOD ALCOHOL DETERMINATIONS FOLLOWING THE INGESTION OF DILUTED ETHYL ALCOHOL IN AMOUNTS EQUAL TO $\frac{1}{4}$ GM. PER KILO BODY WEIGHT IN AIR, AND IN 50% O₂ AND 2% CO₂.

Grams per 100 cc. of blood.																
Condition.	Period, hours.	Kne Series I. II.		Sor.	Eck.	Yan.	Fel.	Sch.	Wal.	Cum.	Art.	Max.	Ben.	Dem.	Har.	Nat.
Alcohol in air	Before*011013012	.014		
	$\frac{1}{2}$.020066	.034036	.050082	.016
	1	.050	.055	.105	.057	.073	.057	.079	.131	.074	.073	.060	.054	.046	.078	.063
	2	.088	.076	.083	.106	.064	.067	.074	.147	.063	.085	.069	.069	.053	.073	.047
Alcohol in 50% O ₂ and 2% CO ₂	Before*013012012	.014		
	$\frac{1}{2}$.061054	.046041	.046053	.065	.039	.041	.083	.080	.036
	1	.075	.037	.064	.178	.030	.050	.074	.039	.072	.072	.069	.057	.073	.078	.038
	2	.055	.051	.035	.103	.051	.039	.075	.059	.077	.057	.052	.034	.057	.069	.024

* Amount of alcohol in the blood previous to the ingestion of the alcohol drink.

Psychological Tests. In Table 6 the average responses are shown for the 14 subjects who took the psychologic tests in air and in high oxygen following the alcohol drinks of $\frac{3}{4}$ gm. per kilo body weight. In general the reaction of each subject after the alcohol drink was better with the 50% oxygen and 2% carbon dioxid than in air. In treating the data for the statistical reliability of the observed difference by Fisher's Method, it was found that the differences were reliable with the exception of the Choice Reaction and Digit Symbol tests in which cases the chances were only 40 to 50 and 60 to 70 in 100 that the high oxygen had a significantly beneficial effect. The improvement in individual cases was very striking. In several of the subjects, however, where the blood alcohol determinations were not significantly different in air and in high oxygen the psychologic tests likewise showed only slight differences if any, for example, Eck and Kne.

The average individual response for each of the 14 subjects in the 6 tests shows a general tendency toward improvement after the ingestion of alcohol in high oxygen as compared to air. Out of 84 chances to perform, improvement occurred in 63 cases (75%); 12 (14%) cases were slightly worse and in 9 (10.5%) there was no significant change.

In comparing the variability of response following the ingestion of alcohol in air and in 50% oxygen with the control series without alcohol, there is an increase in the standard deviation in all tests with the exception of Dotting. After the ingestion of alcohol in high oxygen the average responses were less variable as compared to alcohol in

air. This was especially noticeable in the Choice Reaction, Color Naming and Code tests. In each of these tests the standard deviation is approximately twice as large in air as in high oxygen (Table 6).

TABLE 6.—RESULTS OF PSYCHOLOGICAL TESTS FOR 14 SUBJECTS IN AIR, AND IN 50% O₂ AND 2% CO₂ AFTER INGESTING DILUTED ETHYL ALCOHOL IN AMOUNTS EQUAL TO $\frac{1}{4}$ GM. PER KILO BODY WEIGHT.

	Control air.		Control 50% O ₂ .		Alcohol and 50% O ₂ .		Alcohol air.	
	Mean.	S.D.	Mean.	S.D.	Mean.	S.D.	Mean.	S.D.
Choice reactions . . .	34.4	2.3	35.8	2.9	36.0	3.9	38.6	6.5
Color-naming . . .	48.1	5.9	47.4	7.3	52.4	8.5	61.1	17.5
Pursuit meter . . .	37.9	5.4	35.0	6.2	40.5	10.2	43.9	11.0
Dotting . . .	17.6	2.5	18.1	2.8	17.9	2.4	14.9	2.5
Digit symbol . . .	164.5	24.3	170.3	25.6	157.3	26.8	139.6	29.6
Code test . . .	118.1	12.3	119.7	11.0	122.1	15.2	137.3	27.0

Summary. In this study 23 subjects under various degrees of alcoholic intoxication were tested in an oxygen chamber to determine the value of 50% O₂ and from 0.2 to 10% CO₂ in counteracting the effect of the alcohol. The drinks varied from $\frac{3}{4}$ to $1\frac{1}{4}$ gm. of ethyl alcohol per kilo body weight diluted to a total volume of about 250 cc. or $\frac{1}{3}$ alcohol and $\frac{2}{3}$ water and orange juice. In order to determine the efficacy of the excess oxygen and carbon dioxid in counteracting the effect of the alcohol samples of venous blood were drawn $\frac{1}{2}$ hour, 1 and 2 hours following the drink and analyzed for blood alcohol and lactic acid. The alterations in behavior were studied by a series of 6 psychological tests. The respiration, pulse and blood pressure was taken at regular intervals. Control experiments were run in air and low oxygen with and without alcohol. The results were as follows:

1. The amount of alcohol in the venous blood showed a tendency to decrease while breathing 50% oxygen and excess carbon dioxid as compared to air. In a number of cases the decrease was more than 50%. In 5 of the 23 subjects, however, the decrease was not significant.

2. An increase in the lactic acid of venous blood was observed following the ingestion of alcohol in air. This increase was not as great when the subjects breathed 50% oxygen and excess carbon dioxid. The observed differences were statistically reliable for the group, especially when the subjects reclined throughout the 2-hour period.

3. After the ingestion of the alcohol in air the pulse and blood pressure on the average showed a transient rise followed by a return to the normal or subnormal rate. Following the larger doses there was a fall in the blood pressure and the pulse became smaller in volume. Following the alcohol drinks in 50% oxygen the variations in pulse and blood pressure were not so great. The changes in rate of respiration were not significant. In a few cases, however, the larger amounts of alcohol in air tended to decrease the rate of respiration.

4. There was a general tendency toward improvement in the 6 psychologic tests after the ingestion of alcohol in high oxygen and excess carbon dioxid as compared to air. The variability of reaction also decreased in high oxygen. The average differences for the group of 14 subjects were statistically reliable in the Code, Dotting, Color Naming and Pursuit Meter tests. For the 14 subjects in the 6 tests there was an increase in efficiency while breathing excess oxygen and carbon dioxid in 63 out of 84 possible chances or in 75% of the tests.

Conclusion. The inhalation of 50% oxygen with an increased percentage of carbon dioxid for 2 hours lowered the alcohol and lactic acid contents of venous blood in subjects who had previously ingested from $\frac{3}{4}$ to $1\frac{1}{4}$ gm. alcohol per kilo body weight; this was accompanied by a corresponding improvement in mental and motor behavior. In certain individuals, however, or in about 20% of the subjects tested, these changes did not occur. There is no evidence whether this was due to differences in basal metabolism, general physiological condition or certain physiological idiosyncrasies in rate of oxidation.

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FURTHER STUDIES ON AZOTEMIA FOLLOWING HEMORRHAGE IN THE DIGESTIVE TRACT.

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It has long been well known that increased blood-urea values may be observed in several pathologic conditions besides renal affections. This concerns principally obstruction of the intestinal tract combined with vomiting, certain infectious diseases, especially pneumonia, starvation, deprivation of water, shock and various postoperative conditions.

Even now the explanation of this azotemia, evidently often accompanied by hypochloremia, can hardly be said to be quite satisfactory. Blum¹ has conceived the idea of "l'azotémie par manque de sel," the hypochloremia being to him of primary importance, the azotemia only serving the maintenance of osmotic equilibrium. Still, this theory is hardly tenable, for one thing because of the difference in diffusion power between chlorids and urea.

Frequently an increased toxic destruction of proteins is assumed to cause azotemia; in other cases the dehydration of the tissues is believed to be the cause. It is assumable, however, that the latter causes hypochloremia and a reduced excretion of chlorids, but still the existence of a consecutive relation between chlorids and urea of the blood has not been definitely proved, the frequent simultaneous occurrence of the two conditions, azotemia and hypochloremia, being no proof. On the contrary, the investigations of Courriades⁴ with experimentally hypochloremic dogs prove that hypochloremia is not necessarily accompanied by azotemia.

In addition to the above-mentioned conditions, increase of blood-urea values may be observed in anemia subsequent to repeated severe hemorrhages, as shown by Taylor and Lewis;¹¹ these authors, however, perfectly well understood that anemia itself did not cause the increased values, the increase lasting but a few days and disappearing a long time before the red blood cell counts became normal again. The increase was supposed to be caused by the sudden reduction of the volume of the blood.

Concerning the influence of hemorrhage in the digestive tract on the blood urea, but few observations can be traced. Sanguinetti,⁸ in 9 cases of hemorrhage from ulcers in the stomach and the duodenum observed increased blood-urea values, these being caused, he assumes, partly by an increased destruction of proteins in the body, partly by the resorption of the large quantities of blood accumulated in the intestines. In accordance with this view he succeeds in a few experimental cases in observing increased blood-urea values subsequent to oral administration of blood in normal

persons. In 1935 Clausen³ communicated a similar observation. In Denmark, Christiansen² has recorded 2 cases of severe hemorrhage from gastric ulcers; in both cases considerable increase of blood-urea values was observed together with the cessation or reduction of chlorid excretion in urine. The explanation indicated is the resorption of toxic substances originating from the blood accumulated in the intestinal tract, combined with a diminished supply of chlorids in the food.

Apart from these few observations, all of them made in recent years, no other case of azotemia subsequent to hemorrhage from the digestive tract seems to be recorded. It, therefore, seemed desirable to investigate whether this azotemia appears regularly in hematemesis and melena, or is it a phenomenon observed only in hemorrhages having a violent and perhaps lethal course? Furthermore, I have attempted to study the various circumstances that are supposed to be favorable to the development of azotemia, as no tenable theory, judging from the reports referred to, has been made as yet concerning the origin of azotemia.

Part of this work was reported at the XVII Scandinavian Congress of Internal Medicine, the rest having been made since; but, as all the investigations form a unity, they will here be published in full.

Method. The investigations have been carried out upon 26 patients admitted during the months of March to September, 1935 to the Medical Departments B and C of Bispebjerg Hospital, Copenhagen, suffering from hematemesis and melena. Eighteen of the patients were mentioned in the report at the Congress; 23 were admitted to Department B, only 3 being treated at Department C. The hemorrhage in 22 cases undoubtedly originated from gastric or duodenal ulcers; in 2 cases the cause of the hemorrhage was suspected to be esophageal varices, and this turned out to be evident in a 3d case, as shall be shown later. Finally in 1 case the possibility of cancer could not be disregarded. All patients admitted to Department B were treated in the same way, in accordance with the principles indicated by Meulengracht,⁷ viz.: plenty of food in the form of a full purée diet, ferrous lactate and pulvis alalinus from the very first day of their admission. The 3 patients treated in Department C during the first 24 hours after their admission received only ice-water and coagulen; later they were treated with a rather quickly progressing ulcer diet, individually varying somewhat in the increases.

One of the 26 patients who died will be mentioned separately later. The highest values of blood urea in the remaining 25 patients appear in Table 1:

TABLE 1.—HIGHEST VALUES OF BLOOD UREA.

Blood urea in mg. %.	Cases
Above 70	1
60 to 69	4
50 to 59	7
39 to 49	9
Below 39	—
Altogether	25

From Table 1 it appears that a blood-urea value of 50 mg.% and above, which according to McKay and McKay⁶ must be regarded as absolutely increased, was observed in 12 of the 25 patients; 9 showed a highest value between 39 and 50 mg.%; in 4 patients only, no increase of blood urea above 39 mg.% was observed. It is thus obvious that about half of these patients suffering from hematemesis and melena presented blood-urea values that were absolutely above the normal. It is furthermore evident that in 9 patients values were observed exceeding the limit indicated by McKay and McKay as the general normal highest value: 38 mg. %.

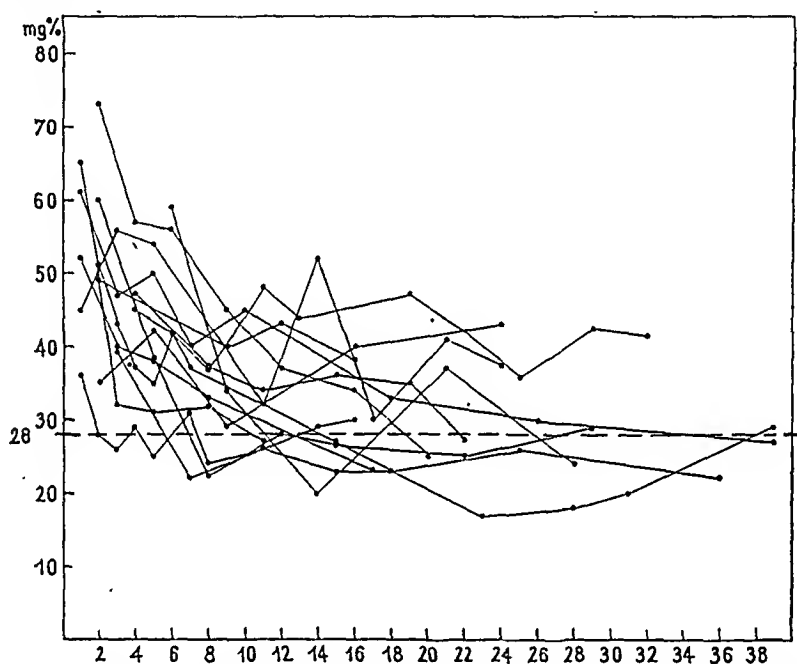


FIG. 1.—Blood urea values in 15 patients; the abscissa indicates days after first observation of hemorrhage.

The observed increase appears more distinctly from Figs. 1 and 2 than in the table. In Fig. 1 the blood-urea values of the 15 patients first observed are plotted graphically, the abscissa indicating in days the time expired since hematemesis or melena was first observed, the ordinate indicating blood urea in mg.%. In Fig. 2 a curve is plotted indicating the average values from the same 15 patients. Fig. 2 shows that the day after the hemorrhage was first observed in these patients an average increase of blood urea up to 52 mg.% was found. Furthermore, it is evident that this azotemia was considerably reduced during the first days, then continuing slightly increased, to return in the course of 3 to 4 weeks to the value regarded as normal according to McKay and McKay, 28 mg. %.

The azotemia has shown no relation to the severity of the anemia, as distinctly appears in Fig. 3; in this figure the abscissa indicates

the hemoglobin percentage, while the ordinate indicates blood urea in mg. %. From the figures representing the 25 patients and corresponding to the highest blood-urea value observed in each patient

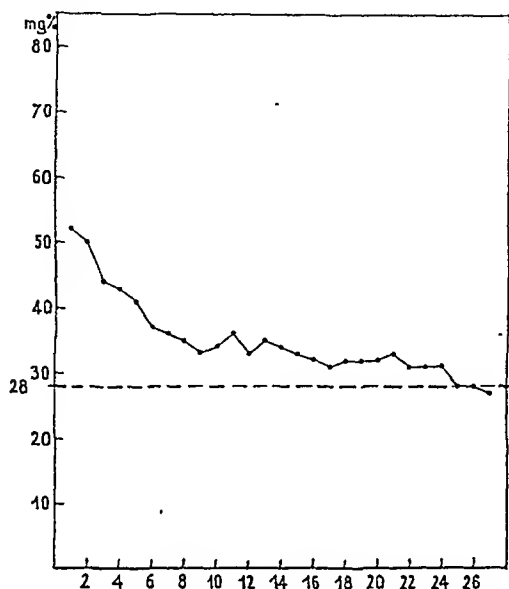


FIG. 2.—Average blood urea values of the above 15 cases.

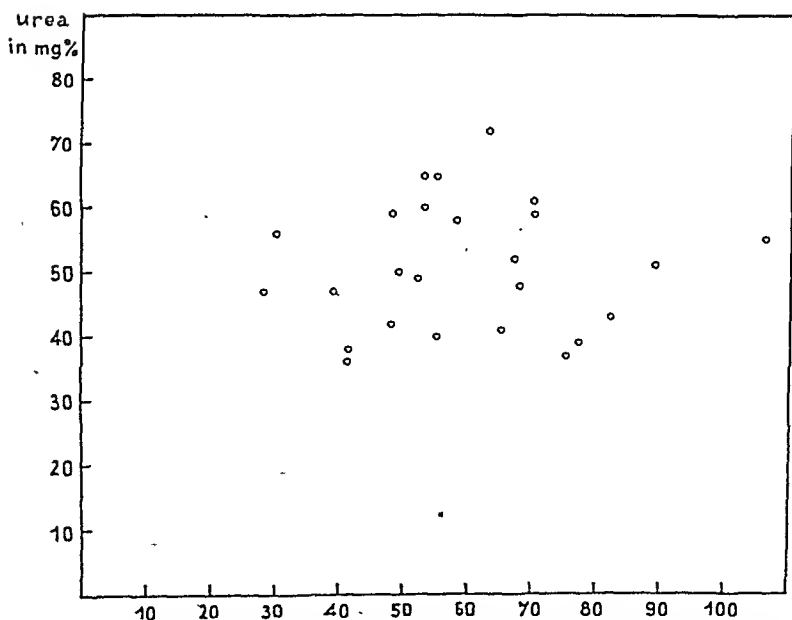


FIG. 3.—Highest values of blood urea in 25 patients and coëxistent hemoglobin percentages.

it is seen that any combination between blood-urea values and hemoglobin percentage may occur; thus increased blood-urea values

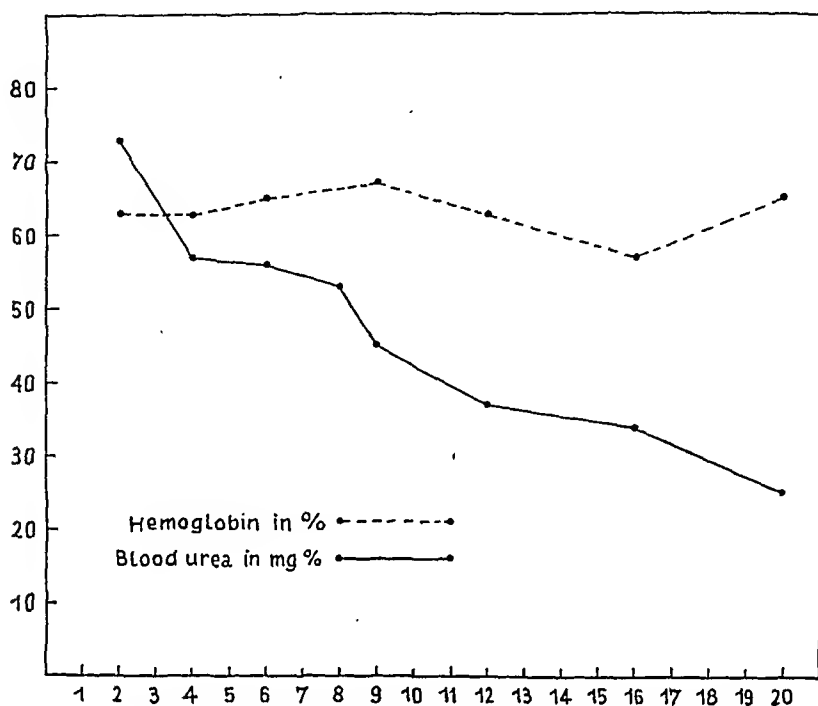


FIG. 4.—Case T. E. J. G., male, aged 42.

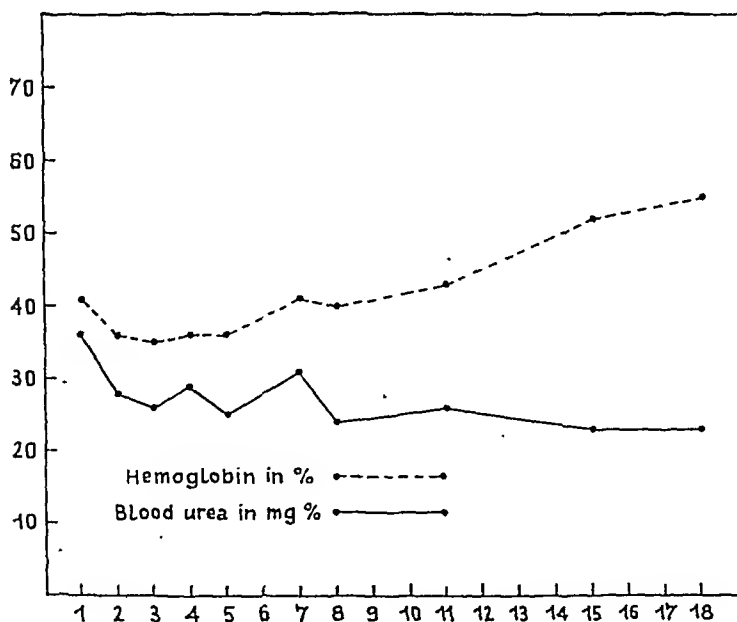


FIG. 5.—Case D. F. G., female, aged 29.

frequently are observed together with normal, or moderately lowered hemoglobin percentage, as shown in Fig. 4. On the other hand,

normal blood-urea values are sometimes found in rather pronounced anemia, as is apparent from Fig. 5.

In contradistinction to the mortality of ulcer hemorrhages, as shown by Meulengracht,⁷ and the regeneration of the blood, as indicated by Schiödt,⁹ both of which have turned out to be excessively dependent on and influenced by the treatment with abundant nutrition, the azotemia has shown no relation to the different methods of treatment. It is true that, as stated, I have only 3 cases treated with ulcer diet, but in these cases the azotemia hardly developed more than in those treated with plenty of food, just as the further course of the azotemia seems to be parallel in all cases.

Only 2 of the 25 patients have been very exhausted, 1 being admitted in a shocked condition, the other gradually bleeding down to a hemoglobin percentage of 21 and 870,000 red blood cells; in both the blood urea was found to be increased up to 73 and 56 mg. %, respectively; against this the remaining 10 patients in whom blood urea exceeded 50 mg. % felt relatively well. Thus no closer relation seems to exist between the extent of the increase and the condition of the patients, at least not within the observed limits.

These observations seem to have established the presence of an increased blood urea; if not very great, at any rate almost invariably, during the first days after hemorrhages in the digestive tract. The cause of it can scarcely be explained with absolute certainty, but the circumstances connected with one of the patients might give a hint:

The patient, a man, aged 53, was admitted June 7, 1934 into Department B suffering from hematemesis and melena. Eight days previously he first observed melena, with daily recurrence. At the time of admission, after having had 2 severe hemorrhages he was extremely exhausted, and during the following days he had several copious tar-colored stools together with frequent vomitings, all of the latter containing large quantities of fresh blood. Because of the vomiting he retained little of the purée diet with abundant fluid prescribed as usual, and, in spite of two transfusions of blood, he steadily grew worse, making a restless uremic impression; he died on the 10th of June, having during the last day and night been almost comatose.

Autopsy revealed about 400 cc. of blood in the stomach, the hemorrhage originating from a burst esophageal varix. A cirrhosis of the liver was also found, together with multiple small abscesses in the liver, both of which were assumed to have contributed to the development of the varices. Microscopic examination of the kidneys showed slight arteriosclerotic changes, otherwise nothing abnormal. The various examinations appear in Table 2.

From Table 2 the rise in blood urea is apparent. The decreased urea excretion was caused both by the reduced diuresis and by the reduction of urea concentration in urine. The chlorids in the urine, already reduced to about half of the normal value, the next day only amounted to 1/20 of the normal value. The heavy reduction of urea excretion might be suggestive of a reduced renal function, and accordingly the urea clearance was determined, the first day giving 80% of the normal value, the following day only 15% of the normal. During the last 2 days the various examinations could not be made, the patient being very restless and urinating involuntarily; the last day anuria practically set in.

TABLE 2.—DATA ON CASE, M. P., MALE, AGED 53.

	Date:	6/7.	6/8.	6/9.	6/10.
Days after first hemorrhage		8	9	10	11
Hemoglobin percentage		50	44		
Red blood cells, in millions		2.48			
Diuresis in cc.		555	330	ea100	0
Urea in 24 hours' urine in mg.%		2580	580		
Excreted urea in grams		14.3	1.91		
Cl in 24 hours' urine (as NaCl) in mg.%		525	66		
Excreted Cl (as NaCl) in grams		2.61	0.22		
Blood urea in mg.%		51	97	148	216
Urea clearance in %		80	15		
Blood pressure in mm. Hg.	75/60	60/40	

According to these observations it seems permissible to explain the increase of blood urea together with the clinical symptoms of uremia as being caused by the reduction of the renal function. According to Van Slyke and coworkers,¹² the clinical symptoms of uremia set in when the urea clearance is reduced to 5% of the normal. This agrees fairly well with the morbid process in this patient, his uremic condition not beginning until the third day, the urea clearance at that time being most likely considerably below the 15% of the preceding day.

Now what causes the reduction of and finally the total cessation of the renal functional? As stated, no evidence was found microscopically of any organic renal affection of importance, and no pathologic elements were found in the urine. There must have been thus a functional reduction of the renal function. As is seen from the table, however, the blood pressure was lowered to about the point where a considerable diminution of filtration in the glomeruli sets in, according to Lassen.⁵ Therefore, the possibility cannot be dismissed that here the lowered blood pressure by means of greatly reduced filtration has caused the observed reduction of renal function. This caused the azotemia and was contributory to, if not directly causing, death. It is conceivable that a possible resorption of toxic substances from the intestinal tract and a dehydration of the tissues may also have had some bearing on the development of azotemia; the practical cessation of the excretion of chlorid suggests the existence of such processes. It cannot now be decided whether a possible injury of the liver may have been contributory, but it may be recollected that in pathologic conditions with an injured liver, *e. g.*, acute yellow atrophy of the liver, lowered blood-urea values are generally found, indicating a diminished capacity of urea formation in the liver (Stadie and Van Slyke¹⁰).

According to the aforesaid observations, however, severe azotemia as just described does not develop in the usual case of hematemesis and melena. The question is, then, if the increase of blood urea generally observed is produceable in a manner similar to that in the case described. In order to get this question answered if pos-

sible I have studied the renal function in 4 other patients. The first was admitted 1 day after a small hematemesis. The results appear in Table 3:

TABLE 3.—DATA OF CASE, C. J., MALE, AGED 55.

Date:	6/10.	6/11.	6/12.	6/13.	6/14.	6/15.	6/16.	6/17.	6/18.
Days after hemorrhage	1	2	3	4	5	6	7	8	9
Hemoglobin percentage	89	89	89	89	89	89	87	87	87
Red blood cells, millions	4.45	4.45	4.90	4.90	4.90	4.90	4.02	4.02	4.02
Diuresis in cc.	500	1435	930	1970	1450	1580	730	1200	915
Urea in 24 hours' urine mg. %	1640	1260	1300	1140	1060	1460	2600	1460	1460
Excreted urea in grams	8.20	18.71	12.09	22.46	15.37	10.95	31.20	13.36	13.36
Cl in 24 hours' urine mg. %	107	170	232	482	627	794	398	419	419
Excreted Cl in grams	0.54	2.53	2.16	9.50	9.09	12.35	4.78	3.83	3.83
Blood urea in mg. %	51	43	37	35	42	37	34	34	34
Urea clearance in %	73	37	190	90	133	121	158	158	158

N.B.—The figures in the first column refer to 12 hours only.

Table 3 shows that though it was a case of hematemesis not exercising any influence on the hemoglobin percentage, blood urea was found to be increased to 51 mg. % together with a reduced chlorid excretion. Urea clearance is a little lowered in the first two determinations, whereafter it is about or above the normal limit. It must, furthermore, be noticed that the blood pressure was quite normal all the time.

The second patient was admitted 4 days after melena was first observed.

TABLE 4.—DATA OF CASE, E. V., FEMALE, AGED 25.

Date:	6/13	6/14	6/15	6/16	6/17	6/18	6/19
Days after hemorrhage	4	5	6	7	8	9	10
Hemoglobin percentage	48	48	48	48	48	48	43
Red blood cells in millions	2.615	2.615	2.615	2.615	2.615	2.615	2.815
Diuresis in cc.	1075	680	875	1420	800	1245	1370
Urea in 24 hours' urine in mg. %	3500	3420	1340	1300	950	720	720
Excreted urea in grams	37.63	23.26	18.93	10.40	12.20	9.86	9.86
Cl in 24 hours' urine in mg. %	398	514	440	1198	378	294	294
Excreted Cl in grams	4.28	3.70	6.25	9.34	4.71	4.03	4.03
Blood urea in mg. %	42	30	26	49	27	27	27
Urea clearance in %	135	157	117	72	138	138	138

N.B.—The figures in the first column refer to 17 hours only.

From Table 4 it appears that blood urea during the first days is only slightly increased, while chlorid excretion is a little lowered, but quickly becomes normal. At the same time a rather considerable urea excretion takes place. Urea clearance is above the normal. On the evening of June 17 the patient felt weak and ill, having epigastric oppression, and next morning blood urea had risen to 49 mg. %, chlorid excretion had fallen to one-third, and urea clearance, which all the time had been about normal value, had fallen to 72%. The following day matters were normal again, except that the chlorid excretion was still somewhat reduced. The blood pressure was normal all the time, but unfortunately was not examined at the time of the slight indisposition.

The third patient was admitted 8 days after the first observation of melena.

From Table 5 it is apparent that, although blood urea in the days immediately after admission was moderately increased, urea clear-

ance was still quite normal. In this case, as in the 2 cases previously reported, the increase of blood urea seems to be of very short duration. And here again the blood pressure was found to be normal at all examinations.

TABLE 5.—DATA OF CASE, V. L., MALE, AGED 51.

	Date:	6/20.	6/21.	6/22.	6/25.
Days after hemorrhage	8	9	10	13	
Hemoglobin percentage	48	45	
Red blood cells in millions	2.39	1.97	
Diuresis in cc.	650	700	700		
Urea in 24 hours' urine in mg.%	3200	2620	2340		
Excreted urea in grams	20.80	18.34	17.38		
Cl in 24 hours' urine in mg.%	357	544	336		
Excreted Cl in grams	2.32	3.81	2.35		
Blood urea in mg.%	59	39	33	
Urea clearance in %	98	131		

NB.—The figures in the first column refer to 12 hours only.

Of a fourth patient, admitted because of several hematemeses during 2 preceding days, it may briefly be stated that, in spite of a hemoglobin percentage of 58 and a blood urea of 58 mg.% at the time of admission, his urea clearance was found to be quite normal in the following days; nor did his blood pressure at any time show anything abnormal.

From these latter observations it seems that the relation between the renal function and azotemia, undoubtedly found in severe cases of intrainestinal hemorrhage, cannot be observed in the slighter cases, which in all cases examined exhibited a normal renal function and an unimpaired capacity for urea concentration. The transitory reduction of urea clearance mentioned in Table 4 thus seems to be of no importance. Consequently the azotemia in these slighter cases must be explained in some other way, such as by the intestinal resorption and dehydration causing toxic destruction of proteins.

In the severe cases, however, the functionally reduced renal function caused by lowered blood pressure seems to be of decisive importance in the development of azotemia, resorption and dehydration alone scarcely being able to cause an increase of blood urea as great as that described.

Summary. It is demonstrated that for days after hemorrhage in the digestive tract increased blood-urea values are generally observed. Of 26 patients suffering from hematemesis and melena, absolutely increased values (*i. e.*, above 50 mg. %) were found in 13; while in 9 other patients values between 39 and 50 mg. % were observed; in 4 patients only no increase above 38 mg. % was found.

In 1 of the patients blood urea was found to be increased up to 216 mg. %, and he died 4 days after admission, with uremic symptoms, without any apparent organic renal affection. At the same time, however, there was a heavy reduction of urea clearance and a very low blood pressure; for this reason the theory is advanced, that the

observed increased blood urea at least partly is due to a functional reduction of the renal function, caused by the low blood pressure.

In order to investigate whether the increase of blood urea found in the slighter cases of intrainestinal hemorrhage might have been due to a similar mechanism, the renal function was determined in 4 patients suffering from hematemesis and melena, but in these cases no reduction was found. It is therefore assumable that the increase of blood urea in these cases is caused by resorption of blood in the intestine and by dehydration of the tissues.

Since the completion of this paper two others, dealing with the same subject have appeared, Sučić, D.: *Akute Azotämie bei grossen gastro-intestinalen Blutungen*, Klin. Wchnschr., 14, 1316, 1935; Ingegno, A. P.: *The Elevated Blood Urea of Acute Gastro-intestinal Hemorrhage and Its Significance*, Am. J. Med. Sci., 190, 770, 1935.

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THE EXCRETION OF FERROCYANID IN MAN IN RELATION TO THE UREA CLEARANCE.

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It is desirable in the study of renal function that at least one method be available which bears a direct relation to the amount of glomerular filtration. Stieglitz and Knight,¹ with this in mind, have proposed that the rate of excretion of sodium ferrocyanid be used

as an index of renal function. They found that following the intravenous administration of about 0.25 gm. of anhydrous sodium ferrocyanid normal individuals excreted 11 to 25% in 1 hour, 20 to 38% in 2, and 26 to 52% in 3 hours. Patients with known renal insufficiency excreted traces or none. In a group of hypertensive patients the excretion was considerably less than in the normal group. The patients with hypertension had little impairment of renal function as measured by the 2-hour phenol red excretion, although somewhat more impairment is deduced from their graphs of the phenol red excretions in shorter periods. The authors felt that the patients in the hypertensive series had diminished renal function, particularly as regards efficiency of glomerular filtration.

The present report is concerned with additional evidence relating to the ferrocyanid test, with particular regard to a comparison of ferrocyanid excretions with urea clearance levels.

Material. The subjects were selected for the test to provide as wide a range of urea clearance levels as possible, rather than on the basis of the type of disease present. Of the 102 tests on which most of the discussion is based, 19 were in subjects free from renal or vascular disease, 23 were in patients in various stages of glomerulonephritis, and 60 were in patients with arteriosclerotic Bright's disease, chiefly primary hypertension. Several of the last group had myocardial insufficiency.

Method. The tests were carried out in the morning. Breakfast was omitted and water was administered freely enough that in most instances a maximum clearance,² i. e., a urinary output of 2 cc. a minute or more, was obtained. The subject voided and the time was noted. Within a few minutes 0.5 gm. of hydrated sodium ferrocyanid,* equivalent to 0.27 to 0.29 gm. of the dry salt, was administered intravenously in 10 cc. water, and the time was noted. Urine was collected after 1, 2, and 3 hours, and blood was withdrawn for urea determination after 1 hour. A large aliquot of each of the urine specimens was titrated for ferrocyanid by the copper sulphate method described by Stieglitz and Knight.¹ The ferrocyanid excretion was expressed in per cent of the content of one ampule; titration of a few ampules from each batch was necessary to provide the standard. The urea concentrations of the blood and urine were determined gasometrically³ and the urea clearance was calculated for each of the first two collection periods. Clearances were corrected for height⁴ and expressed as per cent of normal, 54 cc. a minute being regarded as 100% for standard and 75 cc. as 100% for maximum clearances.

In dealing with urines containing more than traces of blood the method was altered somewhat from that advised by Stieglitz and Knight. When known amounts of ferrocyanid are added to urine containing blood and protein and the protein is precipitated by boiling there is a varying loss of ferrocyanid from the filtrate. Recovery of known amounts of ferrocyanid within 4% was obtained if the urine was refrigerated promptly and centrifuged within a few hours of voiding, and if aliquots of the supernatant urine were titrated while cold. This procedure was followed, therefore, in patients with hematuria. At times there had been enough hemolysis that the endpoint could not be obtained and the test had to be discarded.

Toxicity. Undesirable reactions were few and never serious. In 3 of 122 tests there was nausea for less than 30 seconds after the cessation of the

* Sterile sodium ferrocyanid was furnished in ampules through the courtesy of the Abbott Laboratories.

injection. This may have been due to undue speed in administration. Four men, 3 with mild symptoms of prostatic obstruction, complained of dysuria, urgency and frequency lasting several hours. In one instance there was complete inability to void for 14 hours. More recently administration of ferrocyanid has been avoided in patients with symptoms of prostatism.

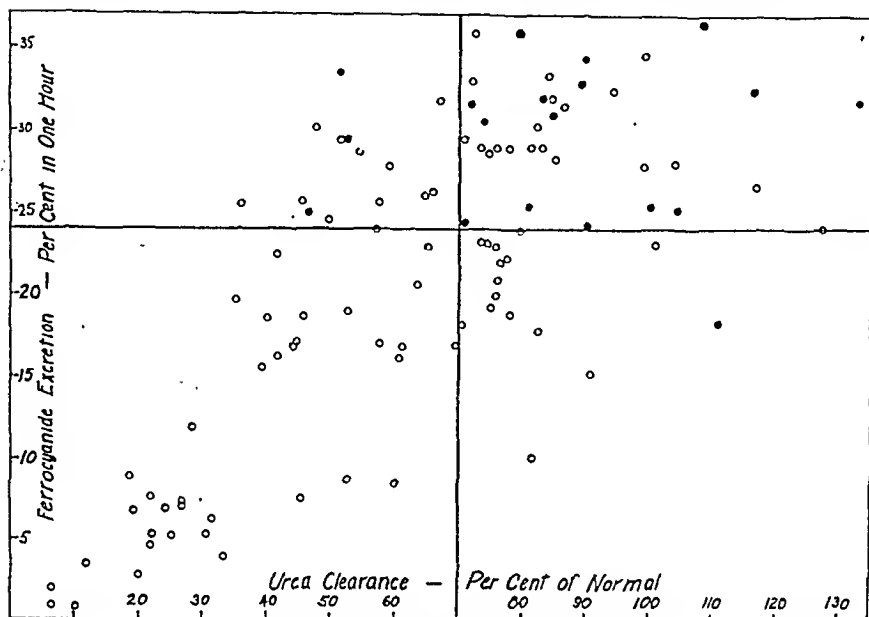


FIG. 1.—Mean clearance and 1-hour ferrocyanid excretion in 102 tests. Solid dots represent normal subjects.

RESULTS. Figure 1 shows the distribution of various levels of ferrocyanid excretion in 1 hour with reference to the mean level of urea clearance. A line is drawn at 70% clearance, which may be regarded in general as a lower limit of normal function, although occasional subjects who are apparently well at times have clearances below this figure. Another line is drawn to correspond with a ferrocyanid excretion of 24% for purposes of further comparison. Graphs of the 2 and 3-hour excretions in comparison with the mean clearances do not differ in any essential from the graph of the 1-hour excretion. The distribution of various ferrocyanid excretion levels with reference to urea clearance is tabulated in Table 1.

Excretion of ferrocyanid in normal subjects generally exceeded 24% in 1 hour, 35% in 2, and 50% in 3 hours (Fig. 1, Table 1). These levels were reached by a considerable number with moderately diminished (30 to 70% of normal) clearance as well. The urea clearance indicates impairment of renal function as a rule in those subjects who excrete less than 18% in 1 hour, 30% in 2, and 40% in 3 hours. Those in whom the ferrocyanid excretion exceeded 18% in 1 hour and failed to reach 24% were predominantly hypertensive patients with moderately diminished or low normal urea clearances.

TABLE 1.—FREQUENCY OF VARIOUS FERROCYANID EXCRETIONS IN PATIENTS CLASSIFIED ACCORDING TO MEAN UREA CLEARANCE.

	Urea clearance less than 30%.	Urea clearance 30% to 70%	Urea clearance 70% or more.
Total number 1-hour tests	15	36	51
Number in which ferrocyanid excretion was above 15%	0	30	50
Above 18%	0	22	48
Above 24%	0	15	36
Total number 2-hour tests	15	36	51
Number in which ferrocyanid excretion was above 20%	1	32	51
Above 30%	1	23	47
Above 35%	0	20	42
Total number 3-hour tests	12	33	51
Number in which ferrocyanid excretion was above 30%	1	28	51
Above 40%	0	22	49
Above 50%	0	12	38

Those subjects who excreted more than 24% of ferrocyanid in 1 hour and whose clearances were above 70% of normal were normal subjects or hypertensive patients without signs of renal impairment. Those in whom the tests were concordantly low uniformly had glomerulonephritis, advanced hypertension, or advanced arteriosclerosis. The subjects in whom the results of the tests were discordant are listed in Table 2, with additional data. The majority of these were patients with glomerulonephritis or hypertension, although 4 apparently normal individuals were included.

Subjects of 32 tests had urea clearances without injection of ferrocyanid within a few days of the combined test, or, in a few instances, during the hour preceding the injection of ferrocyanid. The clearance levels were higher with the combined test in 17 and lower in 15; in no case were variations of significant degree.

In Figure 2 are represented 1-hour ferrocyanid excretion and mean urea clearance in subjects in whom there were repeated tests. The agreement of the two tests is apparently no greater in a single individual at different times than in the series as a whole.

In order to choose the optimal time of measuring ferrocyanid excretion the mean urea clearance for the 2 hours was correlated with excretion in 1, 2, and 3 hours respectively by the Pearson product-moment formula.⁵ A correlation of about 0.7 was found in each instance (Table 3). Because of the fact that there are differences in the clearance from 1 hour to another, a comparison was also made of the first hour ferrocyanid excretion with the clearance during that hour. The correlation was increased slightly, not significantly, above that with the mean clearance for the period. It being theoretically possible that the second hour excretion might be a more stable measure than the first, the second hour excretion was calculated for each individual as a fraction of the ferrocyanid remaining

in the body at the end of the first hour. These quantities correlated much less with the clearance than did the cumulative totals and are probably of no clinical value.

TABLE 2.—DATA ON SUBJECTS IN WHOM THE TESTS WERE DISCORDANT.

	Ferrocyanid above 24% in 1 hour, clearance below 70% of normal.		Ferrocyanid below 24% in 1 hour, clearance above 70% of normal.	
	Age.	Remarks.	Age.	Remarks.
1. Discrepancy slight	28	Acute glomerulonephritis	53	Hypertension known 4 yr.; albumin and casts in urine intermittently.
	52	Hypertension known 15 years, traces of albumin in urine intermittently	59	Peripheral arteriosclerosis, systolic hypertension; normal urine.
	58	Hypertension of uncertain duration, no albumin	67	Hypertension known 3 yr.; occasional erythrocytes in urine, no albumin.
			54	Hypertension known 4 yr.; albumin and casts in urine intermittently.
2. Tests on other occasions concur in good function	34	No renal or vascular disease; mild diabetes	57	Hypertension known 4 yr.; albumin and casts in urine intermittently.
			30	Intermittent albuminuria, few erythrocytes in urine.
3. No other tests, clinical history negative	34	Psychoneurotic; no renal or vascular disease	54	Functional colitis; no renal or vascular disease.
	51	Functional colitis; no renal or vascular disease		
4. Tests on other occasions concur in poor function	38	Acute glomerulonephritis	38	Acute glomerulonephritis.
	39	Acute glomerulonephritis	19	Acute glomerulonephritis.
	23	Chronic active glomerulonephritis		
	50	Hypertension known 6 yr.; renal infarct (?)		
5. History of renal or vascular disease without clinical renal insufficiency	27	Hypertension 11 yr., no albuminuria	39	Latent glomerulonephritis; albuminuria and hematuria persistently.
	29	Mitral stenosis; traces of albumin in urine; no evidence of myocardial insufficiency	68	Generalized arteriosclerosis, Stokes-Adams syndrome; 1 urine negative; died.
	53	Hypertension more than 10 yr.; no albuminuria	62	Hypertension known 3 yr.; cerebral hemorrhage; traces of albumin in urine intermittently.
	64	Arteriosclerosis; anemia, probably primary; albuminuria constantly	59	Hypertension known 5 yr.; urine always normal, concentrates to 1.030.
	47	Hypertension known 3 yr.; occasional trace of albumin in urine	50	Arteriosclerosis, systolic hypertension; traces of albumin in urine intermittently.
			64	

TABLE 3.—CORRELATION COEFFICIENTS.

Mean clearance—1-hour ferrocyanid	0.712
Mean clearance—2-hour ferrocyanid	0.690
Mean clearance—3-hour ferrocyanid	0.713
First hour clearance—first hour ferrocyanid	0.718
Mean clearance—second hour ferrocyanid (expressed as a fraction of the remainder after first hour)	0.588

Discussion. Evaluation of a renal function test may well be approached from two standpoints. A knowledge of the physiology of the test makes it possible to make certain deductions as to the significance of variations; on the other hand a knowledge of the

other clinical findings with which the results are associated is required to establish the correctness of the deductions. It is also desirable to determine whether the procedure itself affects renal function; whether the procedure is safe; and whether it is simple enough for general use.

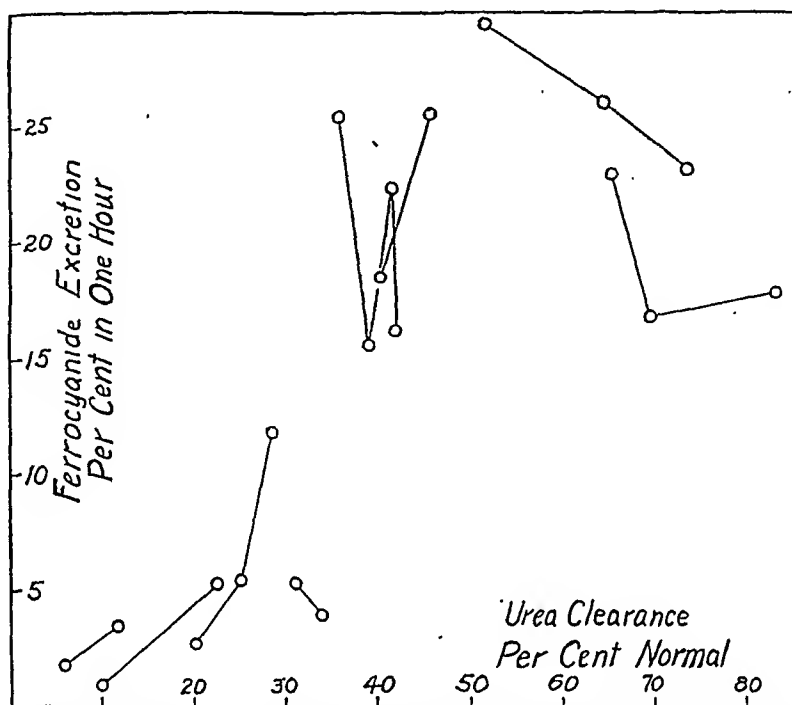


FIG. 2.—Mean clearance and 1-hour ferrocyanid excretion in repeated tests on 8 subjects.

On the theoretical side, the chief point of interest is the relation of the test to the amount of glomerular filtration. A satisfactory measure of glomerular filtration must fulfill four requirements: (1) the substance used must be eliminated by glomerular filtration and in no other part of the urinary tract; (2) it must not be reabsorbed in any part of the urinary tract; (3) the amount eliminated in the urine in unit time must be measurable; and (4) the concentration in the plasma during that time must be measurable.

It is probable that ferrocyanid satisfies the first two requirements sufficiently for practical purposes. Marshall⁶ and Marshall and Grafflin⁷ observed that aglomerular fish excreted ferrocyanid in insignificant amounts. Gersh and Stieglitz⁸ produced histochemical evidence indicating that in the rabbit ferrocyanid excretion is glomerular and that reabsorption in the tubules is either absent or nearly so. Van Slyke, Hiller, and Miller,⁹ using large doses of ferrocyanid intravenously, have demonstrated a plasma ferrocyanid clearance in the dog which parallels closely the simultaneous clearances of creatinin and inulin. Such close correspondence

among three substances so different chemically introduces a strong presumption in favor of exclusively glomerular elimination and lack of reabsorption.

Estimation of ferrocyanid in the urine presents no serious difficulties as a rule. The fourth requirement is not fulfilled in this test. The concentration in the plasma is not, however, entirely uncontrolled; for the relation of body size to the size of the dose injected is important in determining concentration. A certain degree of constancy in plasma concentration can be assumed, subject to variations in plasma volume, body fluid volume, rate of diffusion, extrarenal elimination, and destruction of ferrocyanid. Variations correlated with differences in body size, furthermore, tend to be compensated in a very rough way by differences in kidney size.

It is therefore concluded that the rate of glomerular filtration is a factor in determining the rate at which ferrocyanid is eliminated following the intravenous injection of a known dose. However, the evidence so far fails to establish the rate of excretion under such conditions as a specific test of glomerular filtration.

Clinical evaluation of the test could be carried out ideally by observing a series of patients with progressive renal disease over a period of years and noting the clinical and anatomical phenomena with which changes were associated. This has been done for the urea clearance by several workers, of whom only a few need be cited here: Møller, McIntosh and Van Slyke² and Van Slyke, *et al.*¹⁰ for the clinical, and Hayman and Johnston¹¹ for the anatomical changes. In view of the firm basis on which the urea clearance rests as a test of renal function, a comparison of the ferrocyanid excretion with the urea clearance is justifiable for an immediate estimate of its significance.

The graph (Fig. 1) indicates a definite relation between the levels of the two tests. While the choice of a definite lower limit of normal is an arbitrary procedure, a tentative limit may be set as a point of departure in further analysis. It appears from the graph that 24% excretion of ferrocyanid in 1 hour corresponds approximately to 70% of normal clearance in this series. If 24% be taken as a lower limit of normal, in 72 tests the urea clearance and the ferrocyanid excretion are concordant in revealing either normal or diminished function. These patients are sufficiently classified and require no further discussion.

The 30 discordant tests are equally divided between those in which the urea clearance is below 70% and those in which the ferrocyanid excretion is below 24% (Table 2). In view of the fact that the standards of normal are arbitrarily chosen, 9 may be dismissed as borderline cases in which the discordance is more apparent than real (Group 1). In Groups 2 and 3 it appears that the test giving higher results, and in Group 4 the test giving lower results, is more credible. The tests in Groups 2 and 4 were repeated at short inter-

vals and in no case was there evidence of change in the condition between tests. It will be observed that added evidence supports the urea clearance 5 times and the ferrocyanid test 5 times where there is discordance. Group 5 includes those in whom the evidence is still inadequate for judgment as to which test to believe. Three of the 5 with low clearance, and 4 of the 6 with low ferrocyanid output had albuminuria. The others with low clearances had had hypertension more than 10 years. Group 5 as a whole is clinically a borderline group.

From the comparison of ferrocyanid excretion with the urea clearance and with a view to other findings it is concluded that in the majority of instances patients with renal impairment excrete ferrocyanid more slowly than normal subjects and that the diminution parallels in a general way the diminution in urea clearance. If 24% in 1 hour be considered as approximately corresponding to 70% of normal clearance, the tests are about equally delicate in separating patients into two groups. In a minority of patients the result of either test may be satisfactory when the other is low, and the collateral evidence suggests that the error may be ascribed to either test with about equal frequency in this series. The present work offers no explanation of the physiologic significance of discordant results. The fact that the correlation of ferrocyanid excretion with clearance on the same specimen of urine is not significantly greater than its correlation with mean clearance suggests that the discrepancies are not to be ascribed in any considerable measure to irregularities in emptying the bladder.

Furthermore, it is too early to pronounce final judgment on the clinical significance of the ferrocyanid excretion test until it has been followed for long periods of time in single patients during the progress of renal disease. The value of the test in detecting impairment of renal function may well be considerable without similar value in estimating degree of impairment. The urea clearance has proved particularly valuable in that it is, on the one hand, relatively delicate in detection of impairment; and on the other, applicable to determination of changes in function through a wide range of values practically to the lowest function compatible with life. Progress may be observed in the clearance after the phenol red and specific gravity tests have reached a constant minimum. The accuracy of the ferrocyanid test in observing the progress of renal disease has not been established; not has its applicability been established where excretion is too low to be measured by the titration method used.

Several incidental observations on the test seem worthy of mention. The administration of ferrocyanid does not apparently affect the clearance; the clearance levels in normal subjects in this series cover about the usual range, and there was substantial agreement between the urea clearances with and without ferrocyanid in 32

subjects. There is no need for collection of urine specimens for more than 1 hour, in view of the similarity of correlation coefficients for various times; it may be that the collection period could advantageously be even shorter. The usefulness of the test is seriously limited in two important classes of patients, namely, those with prostatism and those with pronounced hematuria; in the latter group the difficulty is not insurmountable as a rule, but an accurate measure of ferrocyanid cannot be made by the present copper-sulphate method if much hemolysis has occurred. Aside from this difficulty the test is extremely simple and requires no apparatus other than that commonly possessed by any laboratory, nor any skill other than that possessed by the ordinary physician. For this reason the ferrocyanid excretion test promises usefulness particularly for office practice or under conditions where laboratory facilities are limited.

Summary and Conclusions. The ferrocyanid excretion test of renal function was compared with the simultaneous urea clearance in 102 subjects with a range of clearance levels from 6 to 130%. Following intravenous injection of 0.28 gm. of sodium ferrocyanid, normal subjects excreted at least 24% in 1 hour, 35% in 2 hours, and 50% in 3 hours. There was a correlation of about 0.7 between urea clearance and ferrocyanid excretion for each of these three periods. One hour proved to be an adequate length of time for the test. The administration of ferrocyanid did not alter the clearance. In those instances in which the tests gave discordant results other evidence pointed to error in each of the two methods with about equal frequency. The physiologic significance of the test is discussed. Considerable value in detection of impairment of renal function may be expected of the ferrocyanid test, but its value in observing the progress of renal disease cannot be judged yet and is somewhat more uncertain. The test is simple and harmless in most instances. Great care is required in estimating ferrocyanid in the presence of hematuria and some accuracy is sacrificed if much blood is present in the urine. Patients with prostatic hypertrophy had dysuria and inability to void in some instances.

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THE PHOSPHATID CONTENT OF ALBUMINOUS URINE.

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PHOSPHATIDS are believed by Hardy,¹ Chick,² Macheboeuf,³ Went and Faragó,⁴ Went and Goreczky,⁵ Turner and Gibson,⁶ and others to be associated with protein in blood. If a protein-phosphatid combination, physical or chemical, exists in the plasma, one might expect that the proteins excreted by patients with Bright's disease would carry their associated phosphatids with them into the urine. The present work was designed to ascertain whether the phosphatid-protein ratio in the urine of nephrotic patients is comparable to that in the plasma.

Methods. *Recovery of Phosphatid Added to Urine.* Ten cc. of an aqueous emulsion of cephalin from human brain, containing 2.12 mg. of lipid phosphorus, were added to 500 cc. of urine, containing 0.99% of protein. This was concentrated under vacuum (40° C.) to 15 cc., 300 cc. of alcohol ether (1 to 3 mixture) added, refluxed for 1 hour, filtered, evaporated almost to dryness (40° C.), extracted with several portions of petroleum ether and made up to 100-cc. volume. One cc. of this extract was used for the phosphorus analysis. Analyses were done in duplicate. Lipid phosphorus was determined by the method of Kirk.⁷

Another portion of the urine without addition to cephalin was treated in the same manner. Five cc. were employed for phosphorus analysis.

Petroleum-Ether-Soluble Phosphorus in Normal and Albuminous Urine.

First Method. Five hundred cc. of urine were concentrated under vacuum to 50 cc., refluxed with 30 volumes of alcohol-ether mixture (3 to 1) for 1 hour and filtered. The filtrate was evaporated just to dryness below 60° C., and the residue was extracted with several portions of petroleum ether. The extracts were combined and made up to 100 cc. Ten-cc. portions were used for analysis.

Second Method. Protein was precipitated by treating lots of about 5 liters with 100 gm. of trichloroacetic acid and heating the mixture to 38° C. for 2 hours.

The precipitate was filtered off, washed with 1 liter of water, refiltered,

mixed with 10 volumes of alcohol-ether mixture (3 to 1), and refluxed for 12 hours. After filtering off the solvent, the residue was again mixed thoroughly with alcohol ether and refiltered. The combined filtrates were evaporated almost to dryness at 30° C. under vacuum, and the residue refluxed with redistilled ether for 30 minutes. The insoluble residue was treated with ether twice. The ether filtrate was filtered through fat-free filter paper, evaporated at 30° C., and the residue redissolved in boiling petroleum ether.

TABLE 1.—PETROLEUM-ETHER-SOLUBLE CARBON, PHOSPHORUS AND NITROGEN IN NORMAL AND ALBUMINOUS URINE.

Source of urine.	Protein content of urine, gm. per l.	P-E-soluble phosphorus, mg. per l.	P-E-soluble nitrogen, mg. per l.	P-E-soluble carbon, mg. per l.	Material extracted with lipid solvents.
METHOD No. 1.					
Nephrotic stage of nephritis . . .	12.6	88.0	Total urine.
Nephrotic stage of nephritis . . .	16.4	114.0	Total urine.
Nephrotic stage of nephritis . . .	10.0	0.305	Total urine.
Normal . . .	0	0.013	Total urine.
Normal . . .	0	0.054	Total urine.
Malignant nephrosclerosis . . .	1.8	0.306	Total urine.
METHOD No. 2.					
Nephrotic stage of nephritis . . .	21.5	0	0.14	...	Precipitated urine protein.
Nephrotic stage of nephritis	0	2.80	...	Protein-free urine extract.
Nephrotic stage of nephritis . . .	12.1	Trace	0.45	...	Precipitated urine protein.
Nephrotic stage of nephritis	Trace	0.07	...	Protein-free urine filtrate.*
Nephrotic stage of nephritis . . .	10.2	Trace	Trace	...	Precipitated urine protein.†

* Protein-free filtrate was neutralized with ammonia hydroxid before concentration.

† Urine protein was dried at 35° C. then pulverized until it passed a No. 40 mesh sieve. The powder was extracted in a Soxhlet extractor for 24 hours with ether, followed by 24 hours' extraction with petroleum ether. After concentration of the extract to 100 cc., acetone was added (200 cc.) and the mixture placed in the ice box for 12 hours. A very slight precipitate resulted which redissolved in ether. Only traces of nitrogen and phosphorus were found in this solution.

The urine filtrate after precipitation of protein was concentrated at 35° C. under vacuum to 600 cc. This was placed in a continuous fluid extractor and extracted with ether for 8 hours. The extract was evaporated and the resulting oily residue dissolved in petroleum ether.

Petroleum-Ether-Soluble Carbon in Albuminous Urine. Six-cc. samples of urine from 2 patients suffering from the nephrotic stage of chronic nephritis were analyzed by the method of Kirk, Page and Van Slyke.⁸

Petroleum-Ether-Soluble Nitrogen in Albuminous Urine. Lipid nitrogen was determined by the micro-Kjeldahl method, using the new hypobromite reagent of Van Slyke and Kugel,⁹ as described by Kirk, Page and Van Slyke.

Results. Recovery of petroleum-ether-soluble phosphorus in the form of cephalin added to albuminous urine was 79%. The quantities of petroleum-ether-soluble carbon and phosphorus in normal and albuminous urine are given in Table 1.

Conclusions. Nephritic patients losing large amounts of protein in the urine excrete only traces of lipid phosphorus (phosphatids) and lipid nitrogen. Lipid carbon is present in very small amounts.

Lipid phosphorus does not increase in the urine with increase in its protein content.

It appears that either phosphatids are not attached to proteins in the plasma in significant amounts, or that the combination is broken when the proteins are excreted in the urine.

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ACUTE POSTOPERATIVE NECROSIS OF THE LIVER.*

(SOCALLED HIGH-TEMPERATURE LIVER DEATH SYNDROME.)

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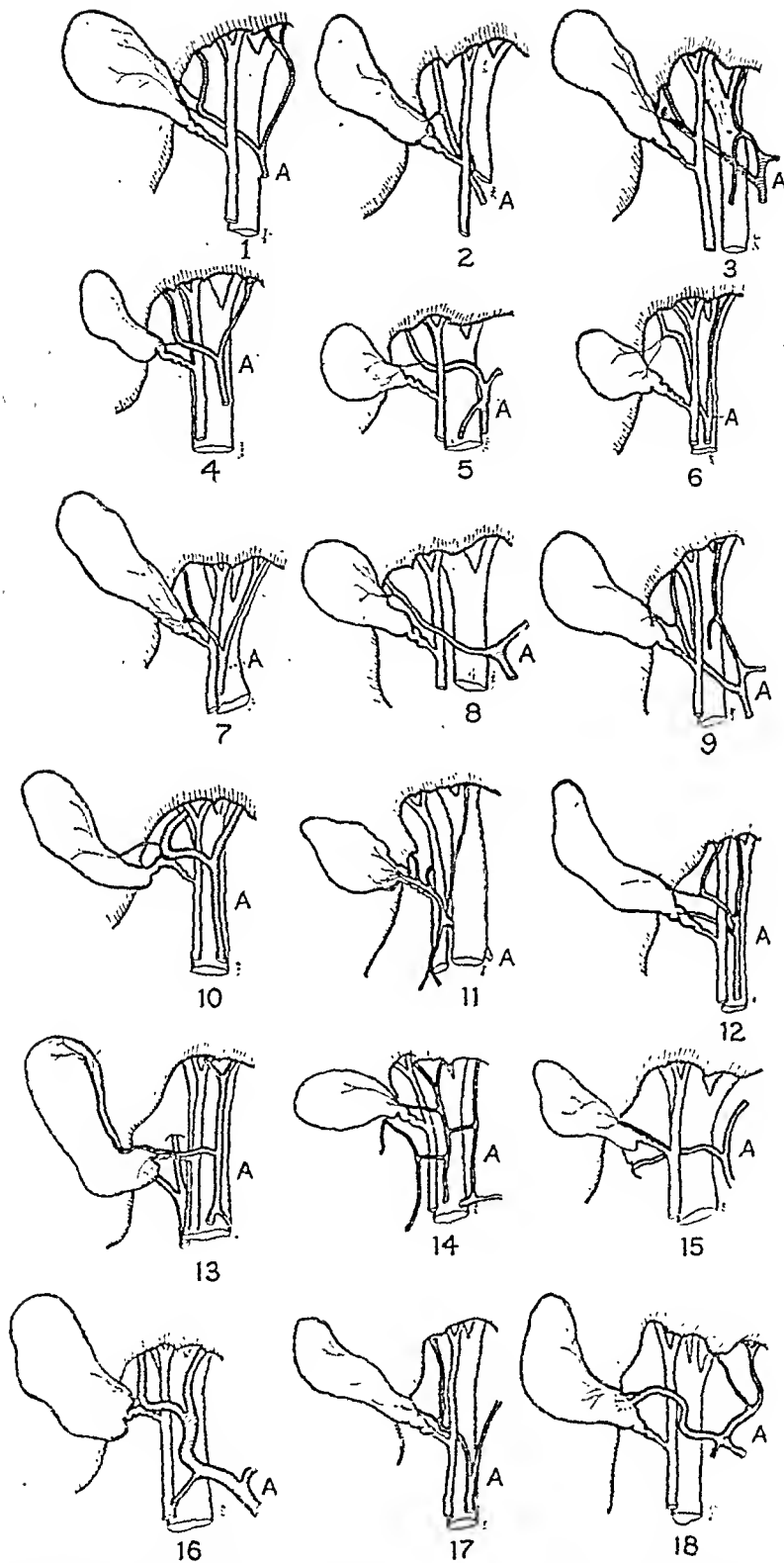
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IN a preliminary report¹ attention was called to the essential clinical features and the lesion in the livers in patients who develop the so-called high-temperature liver death syndrome, and the similarity of the clinical course and liver damage in man dying with this syndrome and in dogs following ligation of the hepatic arteries was noted.

Heyd² first described this postoperative complication which is characterized by sudden, rapid and progressive rise in temperature during the first day after operation, falling blood pressure, rapid pulse, circulatory collapse, coma and death, with a temperature of 107° to 109° F., within 36 to 48 hours. Postmortem examination shows passive congestion, softening, diffuse disorganization of the

* Read before the New York Academy of Medicine, Section of Surgery, April 5, 1935.



FIGS. 1 to 29.—Sketches of dissections of the gall bladder, bile ducts and hepatic artery.
(220) A, artery.

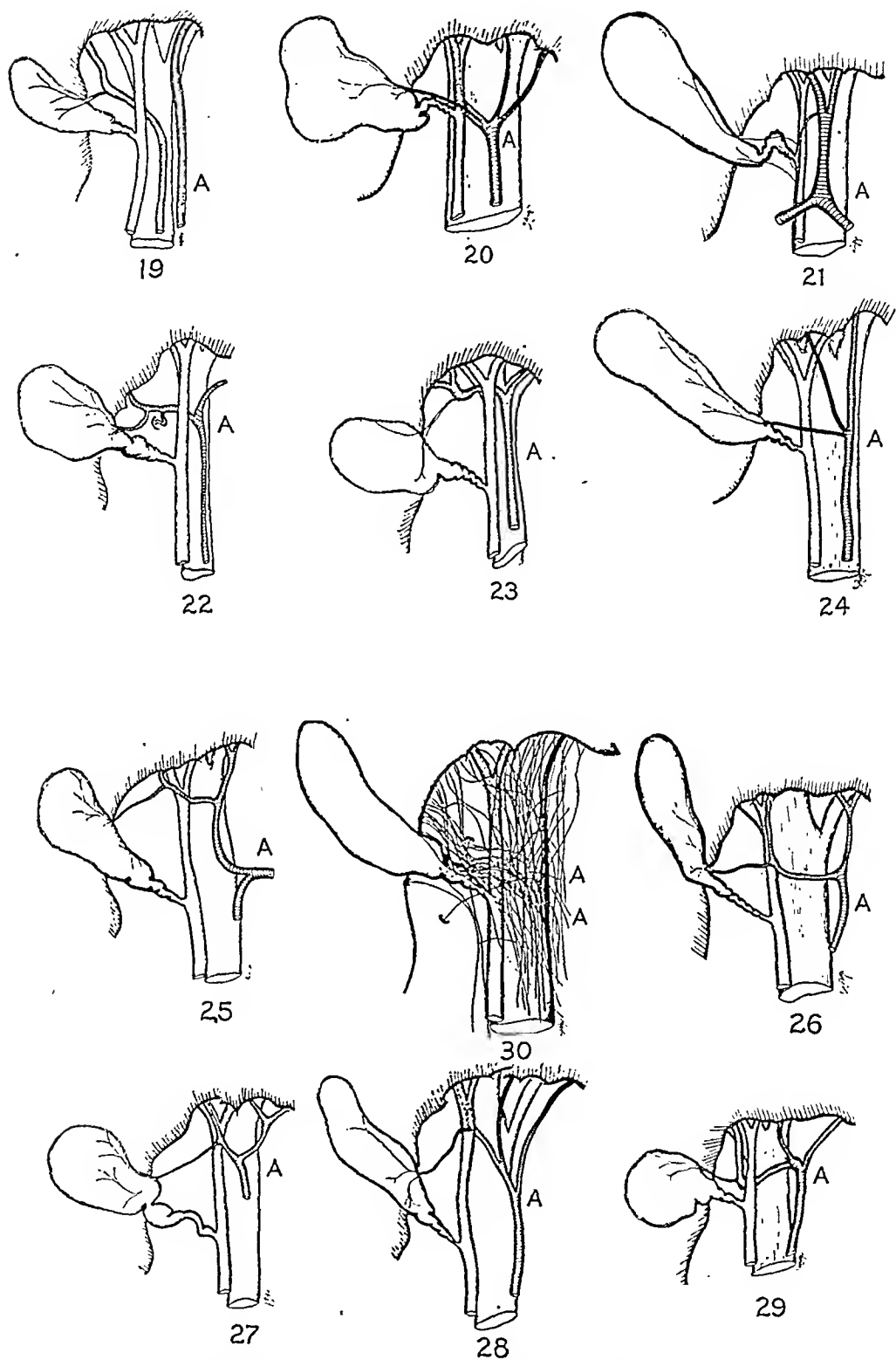


FIG. 30.—Composite drawing of Figs. 1 to 29. The single lines, AA, about the portal vein, bile ducts and cystic duct represent the locations of the branches of the hepatic artery in the 29 dissections.

liver cords with widespread areas of focal necrosis of the liver. From an examination of 23 livers following this type of "liver death," Boyce³ concludes that in most instances when the clinical course was typical the postmortem findings were typical, *i. e.* necrotic changes in the liver with or without similar changes in the convoluted tubules of the kidneys, depending upon how long the patient lived after operation.

Henschen,⁴ in his monograph on the meaning of the liver in surgery, in writing of this postoperative complication, says it is almost conceivable to him that this condition may be due to incidental ligation of the hepatic artery during the course of the operation. Thoreck⁵ believes that 33% of individuals possess accessory hepatic arteries which may be a source of danger. Many investigators have studied the arrangement and distribution of the hepatic vessels and all agree that wide variation is common. The orthodox description found in anatomic texts leads one to believe that the hepatic artery passes toward the liver medial to the common bile duct and anterior to the portal vein; that it divides near the hilum of the liver into a right and a left branch which go to the respective lobes of the liver; and that the cystic artery normally arises from the right branch, passes to the right dorsal to the common hepatic bile duct and thence to the gall bladder. In this arrangement there would be relatively little danger of injuring an hepatic artery while clamping or dissecting the cystic duct.

In dissections of 29 unselected cadavers in the medical and the nurses' training schools during the past year, wide variation in the course and branches of the hepatic arteries was found (Figs. 1 to 29); and in 16, more than 50%, the right hepatic artery was in such close relation to the cystic duct that it might easily have been injured during a cholecystectomy. A composite drawing (Fig. 30) shows graphically the assembled relations of these arteries to the cystic duct.

To determine experimentally the clinical course and the liver changes following ligation of the hepatic arteries 14 dogs were operated upon. Cholecystectomy was performed in all and at the same time dissections were carried out isolating the hepatic arteries. The largest artery was invariably ligated and in many, smaller vessels were also clamped. All of the animals recovered promptly from their ether anesthesia, drank water freely, walked about their cages, responded normally and appeared to be in excellent condition. Six of these dogs developed immediate progressive rise in temperature, which reached 104° and 105° F. (Fig. 31). Five died in less than 36 hours and 1 died during the fourth postoperative day. Although fever reactions are more difficult to obtain in dogs than in human beings, the clinical postoperative course of these dogs was similar to that seen in high-temperature liver death syndrome. In all of the 6 dogs the livers showed diffuse disorganization of the

liver cords and many areas of focal necrosis (Fig. 32). These lesions resemble closely those found in human livers (Fig. 33).

Loeffler,⁶ in reporting further investigations of the results of ligation of the hepatic arteries, concludes that the results are the same in man, the dog and the rabbit . . . and it is immaterial at what point ligation occurs.

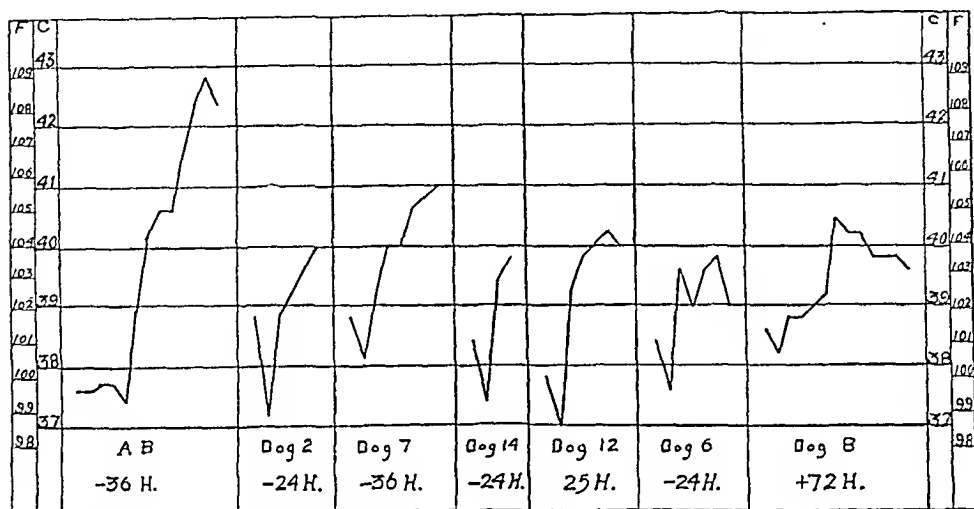


FIG. 31.—A. B. Patient who developed typical syndrome and died in less than 36 hours with the temperature shown. Photomicrograph of his liver, Fig. 33. Dogs 2, 6, 7, 12 and 14 after a fall of temperature during the operation showed progressive ascending temperature and died as the figures under the curves indicate. Dog 8 after showing immediate elevation of temperature lived for slightly more than 72 hours after operation.

In the 8 surviving dogs, none of which showed typical elevations of temperature, injections of a bismuth suspension or a starch mixture demonstrated adequate collateral circulation to all lobes of the liver. In these livers there were areas in which there was disorganization of the liver cords but there was no necrosis. Von Haberer⁷ found in a large series of experiments in which he ligated the hepatic arteries that the animals which lived following the operation were those which possessed this collateral circulation.

Following operations upon the thyroid, in extensive burns and in intestinal obstruction there is occasionally a postoperative course clinically similar to that of high-temperature liver death syndrome. In these cases, while the liver is not involved in the operative procedure, there is hepatic softening and necrosis resembling that found after postoperative liver deaths.

In the presence of chronic and acute cholecystitis and biliary tract disease there are variable degrees of liver damage and operative trauma to the liver or vessels may be sufficient to cause the development of this syndrome. Direct injury to hepatic vessels is a frequent possibility and there might be accidental ligation or trauma

initiating thrombosis. Much work remains to be done, and the pathologist at the postmortem table by careful examination of the hepatic vessels at the hilum and in the substance of the liver may be able to throw additional light upon this problem.

The essential lesion in these "liver deaths" appears to be acute central necrosis of many liver lobules. Renal changes were not found in the experimental animals considered in this paper or in human patients who died within 48 hours of operation. Such kidney damage is secondary to the liver necrosis and requires more time for development. A clinical postoperative course similar to that found in human beings and similar liver changes can be produced in dogs by ligation of the hepatic arteries. While, clinically, vascular occlusion may be due to thrombosis, embolism, or accidental ligation, there are without doubt other as yet unknown factors which bear upon the development of this syndrome. In view of the similarity between the clinical course and liver changes in the experimental animal and in the human beings who develop this postoperative complication, it seems reasonable to apply a pathologically descriptive phrase and call it "acute postoperative necrosis of the liver."

Summary. 1. So-called high-temperature liver death syndrome is a clinical entity characterized by rapid progressive development of high fever, falling blood pressure, circulatory collapse, coma and death with a temperature as high as 109° F. within 36 to 48 hours after operation.

2. The essential lesion in the liver is diffuse central necrosis of the liver lobules.

3. Similar clinical courses and similar liver changes have been produced in 6 of 14 dogs by ligation of the hepatic arteries.

4. In 8 dogs which did not die with this syndrome there was adequate collateral circulation to all lobes of the liver and there was no hepatic necrosis.

5. The similarity in the clinical course and the pathologic changes in the liver in man and dog makes it reasonable to apply a pathologically descriptive phrase and call this postoperative complication acute postoperative necrosis of the liver.

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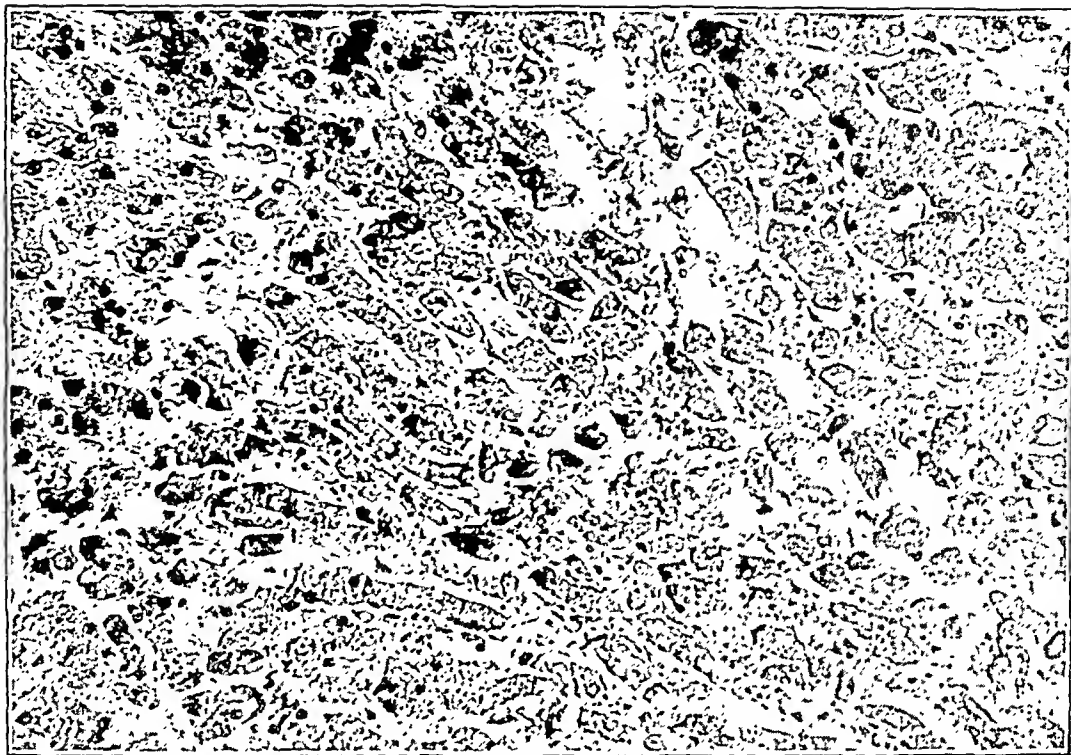


FIG. 32.—Photomicrograph of liver of Dog 7 fixed immediately after death. Note the disorganization of the liver cords and the necrotic liver cells.

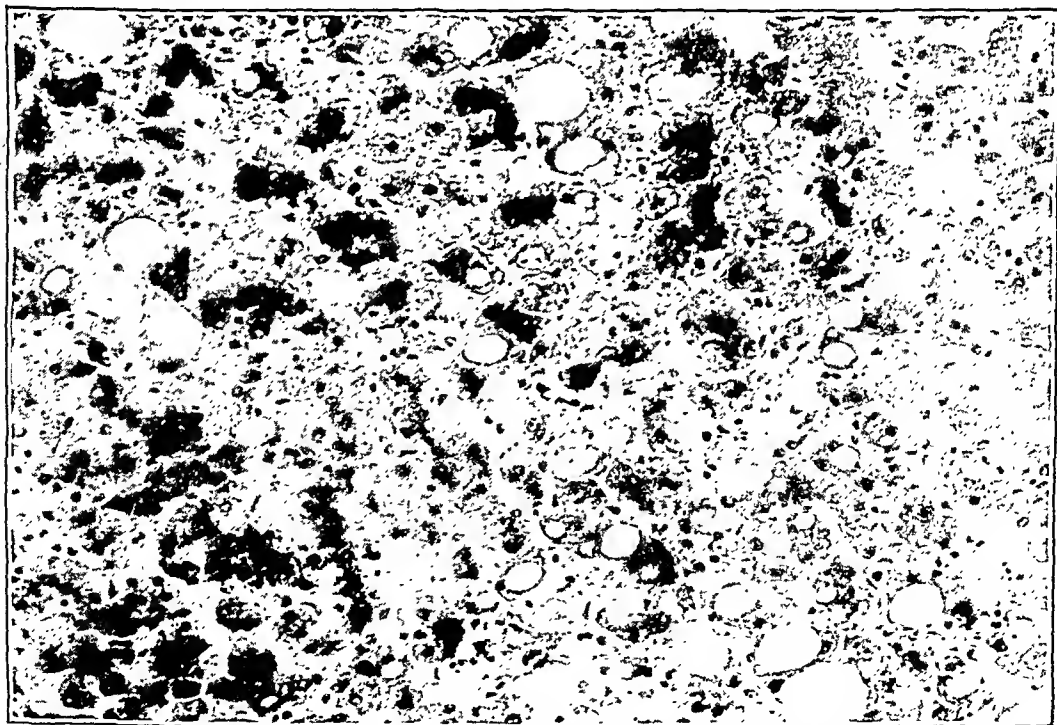


FIG. 33.—Photomicrograph of human liver (patient A. B.). Postmortem examination 1 hour after death. Note the disorganization of liver cords and necrotic liver cells.

ACUTE EPIDEMIC ENCEPHALITIS.

A CLINICAL STUDY OF 160 CASES.*

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DURING the past two decades outbreaks of encephalitis have been reported at various intervals. They have been variously termed encephalitis, encephalitis lethargica, encephalomyelitis and meningoencephalitis. In general, the non-purulent encephalitides have been classified as follows:⁹

- I. Type A encephalitis, or encephalitis lethargica (encephalitis of Economo).
- II. Type B encephalitis or epidemic encephalitis (Japanese form and St. Louis form). Our present group of cases fall into this type.
- III. Post- or parainfectious encephalitis. This includes measles, mumps, whooping cough encephalitis, etc.
- IV. Other forms of encephalitis, such as postvaccinal encephalitis.

Following the influenza epidemic in Italy⁹ during 1889-1891, a disease known as *nona* was described. This simulated, to a great extent, a postinfluenzal encephalitis that was so common during the interval of 1915 to 1925. Von Economo described the typical postinfluenzal encephalitis lethargica in 1916. During the 1915-1925 period, a large number of this type of cases were reported. This is an entirely different form than that which occurred in St. Louis and other epidemics of Type B form.

Several epidemics of Type B^{2,9} have occurred in different parts of the world; but no large epidemic occurred in this country until the St. Louis epidemic in 1933. Japan has had frequent outbreaks. An epidemic occurred in Australia in 1917. No outbreaks of this type have been reported in Europe. In the United States, there were 4 distinct epidemics prior to the present one, but it reached large proportions only in St. Louis, with about 1100 cases. During the fall and winter months of 1919 to 1921, 78 cases were reported in Spokane, Wash. In Indianapolis, Ind., in 1930, 1931 and 1932, a curious outbreak was reported, which was described as meningoencephalopathy. In Paris, Ill., in 1932, 27 cases of encephalitis were reported.

It is our purpose in this paper to describe an epidemic of acute encephalitis that occurred in the Windber, Pa., district during the summer months of 1935. The epidemic began on or about July 14, was at its height from July 27 to August 5, and waned until Septem-

* Read at the Meeting of the Pittsburgh Neurological Society, November 18, 1935.

ber 15, when the last case was seen. During this time we observed 160 cases.

The chronologic history of the epidemic is interesting:

Case Abstracts. The first definitely diagnosed case, seen July 14, 1935, was an adult male, aged 25, who was suddenly seized with pain in the left eye, severe headache and stiffness of the neck. About 6 hours after the onset of these symptoms, he was admitted to the Windber Hospital. Examination upon admission showed the patient to be semistuporous; there was marked cervical rigidity and a bilateral Kernig sign. Spinal puncture showed the fluid to be clear, under increased pressure, positive for globulin, and there was a cell count of 2 cells per c.mm. His headache persisted for 1 week, and he complained of occasional vertigo during this time. Spinal puncture, on July 27, showed 8 cells. He was discharged from the hospital in good condition on July 29. Reexamination, on September 25, showed patient to be in good condition and to be free from any subjective complaints.

The second case, a male, aged 13, was seen on July 19. This was the only fatal case, and we were fortunate enough to obtain an autopsy. The onset was sudden. There was a history of the patient having been swimming on the afternoon of his admission to the hospital. While in the pool, he complained of a severe headache and blurring of vision. He went out of the pool and rested. Very soon afterward he became comatose, and was brought to the hospital in this condition about 5 hours later. There was marked cervical rigidity and a bilateral Kernig sign. There was a spastic paralysis of the right arm and right leg. Spinal puncture revealed a bloody spinal fluid under greatly increased pressure. He died 2 days after admission. Autopsy showed a hemorrhagic meningoencephalitis. (For details, see discussion of pathologic anatomy.)

During the next 2 weeks the epidemic assumed widespread proportions throughout the community. A brother of the patient who died developed the infection on July 25. On July 30, at the height of the epidemic, we saw 15 cases. During the second week of August it began to wane, and the last case was seen on September 15.

Etiology. The disease is undoubtedly a virus infection. During the St. Louis epidemic, Muekenfuss, Armstrong, and McCordock³ isolated a filtrable virus from glycerinated brain tissue of fatal cases. They were able to reproduce the disease in monkeys and mice. As our cases did not seem to be as virulent as the St. Louis type, it was felt that this type might be due to another strain of virus. The disease simulates influenza to a great extent, and one might even consider the fact that it is an influenza-like infection with a neurotropic rather than a pneumotropic virus. The virus must also differ from the one that causes encephalitis lethargica, as the clinical picture and pathology of these two conditions is entirely different.

Epidemiology. The disease is apparently transmitted by human contagion by means of droplet infection. It is very highly contagious and entire families are frequently affected; we have encountered instances in which 4 members of one family were affected. Residents of certain isolated districts of the community developed

the infection within a few days of each other. All of the patients had definite throat changes, tending to corroborate the idea that it is primarily a respiratory disease.

As nearly as could be determined, the incubation period varied from 3 to 10 days; in most cases it was about 4 days. In 1 instance a father developed the disease fully 2 weeks after a child had it, but we felt that his was probably a fresh exposure. In some in-

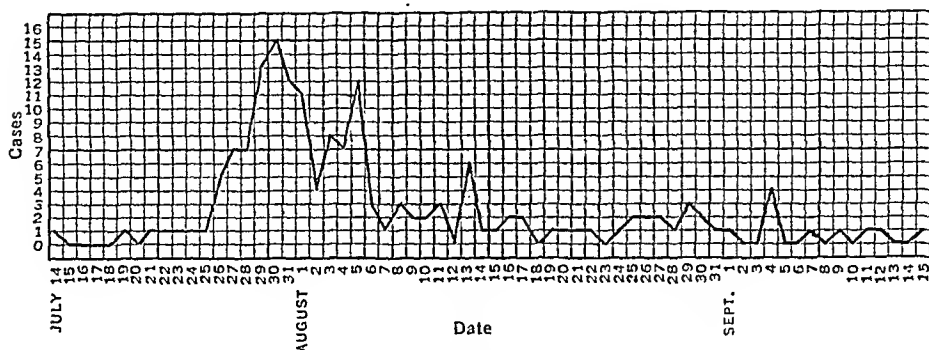


CHART 1.—Distribution of cases according to date of onset.

stances one member of a family would develop symptoms within 1 day after a previous member had developed the disease; but these were probably due to simultaneous exposures. In general, it seems safe to say that the incubation period varied from 3 to 10 days.

Season seems to have a definite influence upon this type of infection. In practically all of the other epidemics the highest incidence was during the late summer and early autumn months.

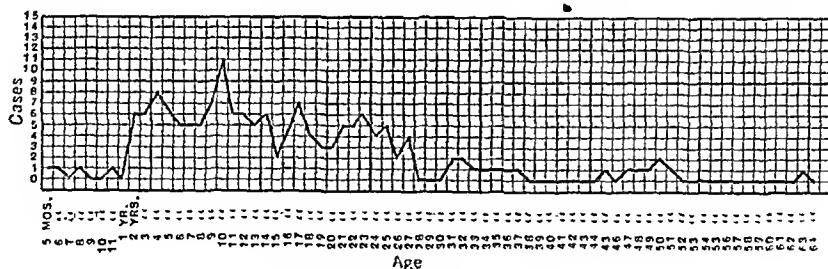


CHART 2.—Distribution of cases according to age.

The infection occurred more in males (98 males and 62 females). Most of the cases occurred in children and young adults; only 17 cases occurred after the age of 30. Young infants seemed to be immune; we encountered only 6 cases in infants under 2 years, and the youngest was aged 5 months. In an effort to determine whether young infants might not be affected with the disease and have vague symptoms, we did spinal punctures on a number of young infants who presented intestinal symptoms, such as vomiting and diarrhea or who had unexplained elevation of temperature. In all

of these cases the spinal fluid examination was negative. In this respect, encephalitis resembles other virus diseases, such as measles, young infants under 6 months being immune, as a rule. The oldest patient in the series was 63 years.

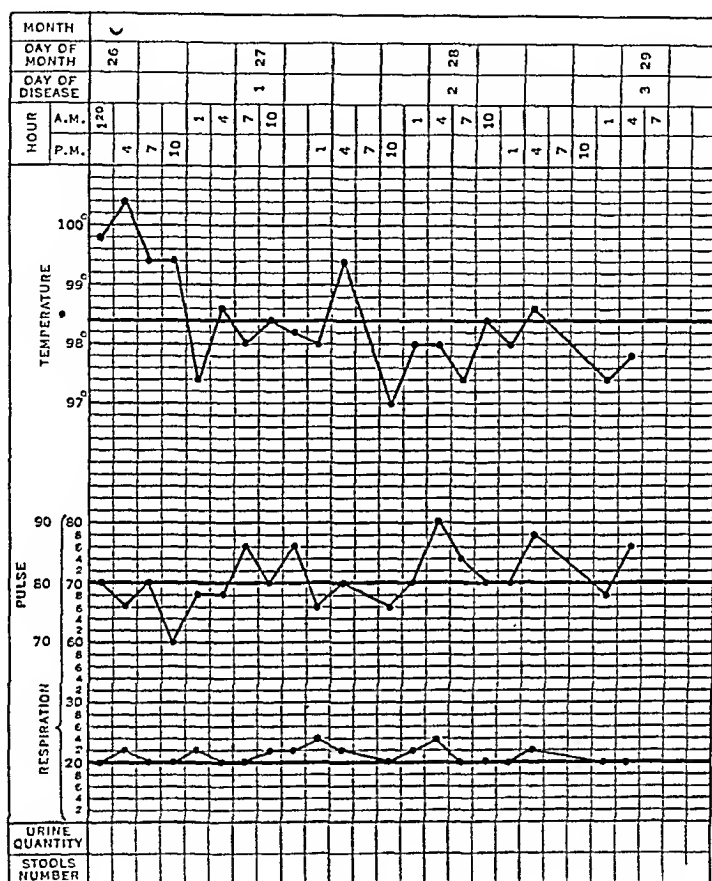


CHART 3.—Temperature, pulse, and respirations of a typical case.

Symptomatology. There was very little variation in the symptoms. Headache and nausea or vomiting were the outstanding symptoms. In a typical case the patient would be seized with a sudden severe headache followed in a few hours by nausea and perhaps vomiting. All of the children had persistent vomiting; many of the adults had only nausea. The headaches were usually occipital and the patients described them as being more severe than any other headaches which they had previously experienced. They also frequently complained of photophobia, pain in the eyeballs, pain in the posterior cervical region, backache, abdominal cramps, muscular pains, nervousness, sleeplessness and vertigo. Muscular pains were encountered very frequently; the vertigo was frequently

persistent and one of the last symptoms to disappear; the abdominal cramps would occasionally simulate an attack of appendicitis. Many patients were relieved of their symptoms while in the recumbent posture, but developed headaches or vertigo while sitting up, or upon any sudden change in posture.

In only 1 case were there convulsions or coma. This was the only fulminating case and the only one in which death occurred.

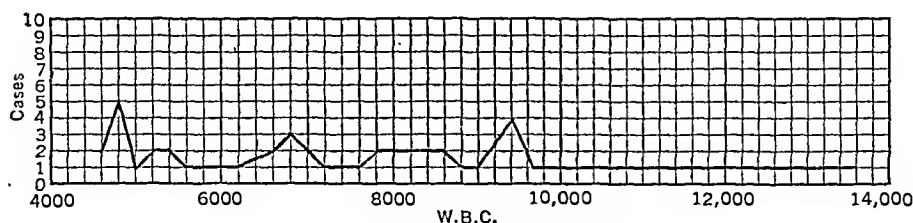


CHART 4.—White blood count in 38 cases.

Physical Signs. In general, there was a notable absence of positive physical signs. Most of the patients did not have any cervical rigidity or positive Kernig sign. In a few of the severe cases with a greater degree of meningeal involvement there was mild cervical rigidity and a moderately positive Kernig sign. Occasionally the pupils were irregular. There were no changes in the abdominal reflexes. One constant positive finding was the typical injection of the soft palate. The soft palate was reddened in all cases and presented a peculiar fine vesicular eruption, giving a strawberry-like appearance. The appearance of the throat differed entirely from that seen in the usual throat infections.

In a few instances there was impairment of the mental faculties. In 1 case there was a hemiplegia.

The temperature varied from normal to 102.4° F. In most cases it was about 101° F. upon admission, and would drop by lysis within 2 or 3 days. The pulse rate was usually slower than one would expect from the temperature record. In some instances there was a marked bradycardia, and in 1 case the pulse rate was as low as 24 per minute.

Blood Findings. There was usually a leukopenia (lowest leukocyte count, 4600). In many cases there was a normal count; in a few there was a moderate leukocytosis (highest, 13,600). There was no disturbance of the relationship of neutrophils to lymphocytes, this, as a rule, being normal.

Spinal Fluid Findings. The spinal fluid findings made on 32 patients, were important. We did not examine the spinal fluid in all cases, as many of the cases were too mild to be subjected to needless spinal punctures. However, during the first few days of the epidemic, spinal puncture was performed on all those suspected. We were amazed to find spinal fluid changes in many patients who

otherwise might be considered to be suffering from gastro-enteritis or a form of influenza. In all but 2 cases the fluid was clear; in 1 case it was opalescent; in 1 markedly bloody. The pressure varied; as a rule, it was increased (15 to 25 mm.); in some cases normal. Globulin was present in varying amounts in all cases. The cell counts were moderately increased; in a few cases they were normal, but in 22 they were over 20 per c.mm. Most of the counts were between 50 and 100; in 1 instance a patient had a cell count of 3 on admission, but 3 days later they had increased to 424; the highest was 670. The cells were 100% lymphocytes. The spinal fluid sugar was normal or slightly decreased.

TABLE 1.—CEREBROSPINAL FLUID CELL COUNTS IN 30 CASES OF EPIDEMIC ENCEPHALITIS. DIFFERENTIAL COUNT: 100% LYMPHOCYTES.

Cell count.	No. of cases.	By groups.	No. of cases.
1	1		
2	2		
3 (later 424)	1	Below 10	6
5	2		
<hr/>			
12	1		
13	1		
23	1		
34	1	10 to 50	9
40	2		
42	1		
44	1		
47	1		
<hr/>			
57	1		
60	1		
67	1		
68	1	50 to 100	9
70	1		
80	1		
87	2		
88	1		
<hr/>			
105	1		
112	1		
117	1	100+	6
122	1		
355 (later 670)	1		
393	1		

Clinical Course. There were 3 types of the disease:

1. The mild or abortive type. In this type the patient would be seized with a sudden, severe headache, vomiting, and moderate elevation of temperature. Vomiting and the headache would subside within 24 hours, and the patient would be perfectly well at the end of 3 days.

2. The moderately severe, or usual type. In this type the initial symptoms were more severe. The patient sometimes presented a picture of collapse. Headaches would persist for possibly a week or more. The temperature would fall by lysis in about 3 days, but

the headaches and vertigo would persist for sometime afterward. This type was occasionally followed by persistent headaches for several weeks. Most of these patients, however, felt well at the end of about 1 week, and have remained free from symptoms thereafter.

3. The severe or fulminating type. Fortunately, there was only 1 case of this type. The onset was sudden; the patient rapidly became comatose, and died 2 days after the onset of symptoms.

Differential Diagnosis. The disease must be differentiated from the following:

1. *Influenza*. The symptoms of influenza frequently simulate the symptoms that we encountered in this epidemic. The headaches were more severe than those ordinarily encountered in influenza. The throat had a characteristic appearance that differed from influenza. Spinal puncture served as a final means of differentiation.

2. *Meningitis*. Symptoms of meningeal irritation were not as common as in meningitis. The spinal fluid pressure was not as great as in meningitis. Tuberculous meningitis usually has a more gradual onset, and does not result in cure as does this illness. It must be borne in mind, however, that most of these cases had some meningeal involvement also.

3. *Poliomyelitis*. The involvement in our cases was cerebral rather than spinal. In no case was there any residual flaccid paralysis. The spinal fluid changes simulated those of poliomyelitis to a great extent.

4. *Encephalitis Lethargica*. The symptoms and clinical course differed considerably from encephalitis lethargica. There was usually no lethargy and there were no postencephalitic sequelæ such as follow the lethargic type of encephalitis.

5. *Appendicitis*. Occasionally the abdominal pain and vomiting would lead one to suspect that the patient was suffering from an attack of appendicitis. However, there was usually no abdominal tenderness. Leukocytosis was usually absent.

6. *Acute Gastroenteritis*. It was difficult to differentiate the disease from gastro-enteritis in many instances, particularly in children. In doubtful cases, spinal punctures would reveal the diagnosis.

After the first group of cases were studied, we were able to establish a group of symptoms and findings which enabled us to diagnose most of these cases without resorting to a spinal puncture. These were as follows: (1) Severe headache and vomiting; (2) characteristic throat findings; (3) leukopenia; (4) history of exposure.

When a patient presented the above history and findings, we felt we were justified in making a diagnosis without unnecessarily subjecting him to a spinal puncture.

Pathologic Anatomy. A postmortem examination was made on 1 case.

Autopsy Findings (Dr. H. A. Slesinger): The dura mater was injected. The entire brain was edematous and its cut surface presented a pinkish color. There were numerous petechial hemorrhages throughout the cerebrum. There was a large area of hemorrhage in the posterior extremity of the thalamus; this had caused erosion into the lateral ventricle and the latter was filled with blood.

Histologic examination of the brain (Dr. R. D. Lillie):

"The leptomeninges present widened spaces without visible contents for the most part. In areas there is extravasation of considerable quantities of partially laked blood, accompanied by a few macrophages and occasional mantling of a small meningeal vessel by lymphocytes. In occasional sulci there is considerable perivascular and interstitial accumulation of neutrophils and lymphocytes.

"The anterior portion of the thalamus shows quite marked capillary congestion, rather numerous corpora amylacea (?) and slight lymphocyte infiltration in the sheaths of a few arterioles. Masses of densely and metachromatically basophilic material similar to the above 'corpora amylacea' occur also in the vessel sheaths in other similarly congested levels of the thalamus. These bodies are quite numerous in some markedly congested areas of white substance.

"In the posterior extremity of the thalamus, adjacent to the cut surface made in severing it from the brain stem there is a considerable area of hemorrhage into the brain substance, surrounding a small artery. Pericapillary hemorrhages are seen about the margins of this hemorrhagic area. Proliferative or inflammatory marginal reaction is absent.

"The hippocampus shows no Negri bodies or other inclusions.

"The corona radiata of the parietal to occipital regions contains several focal perivascular hemorrhages, sometimes of ring form with vessel necrosis centrally. An occasional arteriolar sheath in the occipital region is slightly infiltrated by lymphocytes.

"The gray cortex shows only a slight patchy capillary congestion. There are no lesions in the corpus striatum or corpus callosum.

"The findings are those of an acute hemorrhagic meningoencephalitis."

Prognosis. The prognosis was unusually good. There was 1 fatal case. Of the remaining cases, all but 7 were perfectly well within 2 weeks from the date of onset of their illness. The remaining 7 complained of various symptoms lasting from 3 weeks to 3 months.

Complications and Sequelæ. There were very few complications or sequelæ. There were no pulmonary, cardiac, or renal complications. Seven patients complained of residual symptoms. These included persistent headaches, vertigo, nervousness, sleeplessness, and weakness. At the present time only 1 patient in the entire group has any complaints. This patient, after a period of 3 months, still complains of occipital headaches and vertigo. His headaches

were severe for about 2 months; they are now gradually becoming milder. He has also developed a moderate degree of baldness following his illness. It is certainly too early to state whether or not there will be any delayed sequelæ such as occurred in the post-influenzal encephalitis. However, the experience in St. Louis was that there were no such sequelæ.⁶

Treatment. The treatment varied with the severity of the disease. In the mild cases the patients were treated symptomatically with salicylates and codein and kept in bed for 1 week. The more severe cases were kept in bed for 2 weeks. At first, we did spinal punctures routinely, but subsequent experience proved that those that did not have spinal punctures recovered just as rapidly as those that did. We then performed punctures only on those patients that had persistent headaches for more than 24 hours, or where there were definite signs of increased intracranial pressure.

About 10 days after the onset of the epidemic we started to use convalescent serum (administered intramuscularly) obtained from patients who had recovered from the illness. We used it both prophylactically and in the active treatment of the more severe cases. Twenty-two active cases received a therapeutic dose, which we arbitrarily placed at 7.5 cc. of serum. Although it is extremely difficult to evaluate the results, we felt that these patients recovered more quickly than those that did not have the serum. As stated above, only the more severe cases received the serum, and we found that they would improve at least 24 to 48 hours sooner than those that did not have the serum. None of these patients had symptoms persisting for more than 1 week. The results with serum therapy were more satisfactory if the patient received treatment within 24 hours after the onset of the illness. In 1 case, a child with definite findings of encephalitis was given a dose of serum and was perfectly well within 16 hours. In most of the other cases the patient would begin to improve within 12 hours after the administration of serum and be symptom-free within 24 to 36 hours. However, it must be remembered that many untreated patients also improved very rapidly.

We are positive that convalescent serum has a definite place in prophylaxis of the disease. Prior to the use of serum we were unfortunate enough to have two members of the hospital personnel develop the infection. After the serum became available, we administered 5 cc. of serum to 7 members of the medical and nursing staff who were most likely to be exposed; none of them developed the disease.

Summary. 1. The clinical features of an epidemic of acute encephalitis have been described; 160 cases were seen over a period of 2 months.

2. The disease was highly contagious. It ran a relatively benign course. There were very few residual symptoms.

3. Convalescent serum was of definite value both as a prophylactic measure and in the active treatment of the disease.

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FOREIGN PROTEIN THERAPY.

II. TREATMENT OF UNDULANT FEVER BY THE INTRAVENOUS INJECTION OF KILLED TYPHOID-PARATYPHOID "A" AND PARATYPHOID "B" BACILLI.

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THE object of this paper is to present a series of 12 cases which demonstrate the efficiency of foreign protein therapy in the treatment of undulant fever. The effectiveness of the intravenous administration of foreign proteins in the treatment of this disease has been widely discussed. The usefulness of such substances is assumed to depend upon factors associated with the sharp thermal reaction following their administration.

The treatment we have used with uniform success consists of the intravenous administration of mixed typhoid vaccine,* each cubic centimeter containing 1000 million typhoid bacilli and 500 million each of para typhoid bacilli "A" and "B". The initial dose of 50 million killed organisms was repeated every 5 days until 4 to 6 treatments had been given, the dosage being increased 25 to 50 million each time.

* Eli Lilly Company No. 3V765.

In 1918, Evans¹ demonstrated a close relationship between the serologic behavior of the organisms responsible for undulant fever and Malta fever, and since then these two diseases have been regarded as practically identical. The relationship between this infection in man and contagious abortion in cattle is quite striking, as most cases of undulant fever are traceable to close association either with infected cattle or the consumption of raw cow's milk from contaminated herds.

The incidence of undulant fever in the United States is steadily on the increase. We have seen 12 cases of clinically active undulant fever in the Geisinger Memorial Hospital during the past 5 years in 20,000 general admissions. The United States Public Health Service Statistics² for 1933 show a total of 1788 cases reported in that year and in 1934 there were 2017 reported. The records of the Bureau of Contagious Diseases for the Commonwealth of Pennsylvania³ show 294 cases reported from 1929 to 1934.

The disease presents a fairly characteristic picture by the time medical aid is sought. The onset is variable in type and intensity, ranging from abrupt chills, fever, abdominal pain, nausea, vomiting, acute arthralgia to simple malaise with a low-grade fever which may be overlooked. Men are more often affected than women; 11 of our 12 cases were in men. The usual complaint on admission is weakness, nervousness, loss of weight, arthralgia, fever and epigastric symptoms of varying patterns. Examination of blood for specific agglutinins of *Brucella abortus* is most valuable diagnostically after 2 weeks of illness, although some observers feel that this test frequently remains negative throughout the course of the disease. The intradermal skin test with undulant fever vaccine is helpful in the latter cases. Axel Thomsen,⁴ of Copenhagen, Denmark, found the complement-fixation test to be far more frequently positive than the agglutination tests.

The following case histories illustrate the findings and treatment in this series:

CASE 1.—R. F., white male, aged 8, entered this hospital, August 2, 1934, complaining of weakness, fever, malaise, anorexia, weight loss, generalized muscle soreness, headache and progressive stupor. The temperature fluctuated between 101 and 103. He was in a semistuporous state upon admission which was rapidly progressive for the first few days. He had a bilateral Babinski, fleeting bilateral ankle clonus, absence of abdominal reflexes on the right side. Initial spinal fluid examination showed 175 cells mostly small lymphocytes, 66 mg. sugar and 590 mg. chlorids. Twenty days after admission, his blood was positive for *Br. abortus* in a titer of 1 to 160 (see chart for temperature pattern). He was given his first treatment of 0.05 cc. typhoid mixed vaccine intravenously on the 15th day after admission. His temperature rose to 104° and returned to normal within 24 hours, remaining normal for several days when a slight recurrence was noted, so a second injection was given. Convalescence was rapid and dramatic. Within 24 hours after his first treatment the mentally lethargic state cleared rapidly. He was discharged from the hospital August 31, 1934, in good physical

condition. Check-up examination February, 7 1936, showed a normal child whose blood gave a negative reaction for *Br. abortus*. This case was of especial interest in view of his encephalitic manifestations.

CASE 2.—H. A. B., white male, aged 40, entered this hospital July 29, 1934, complaining of weakness, daily temperature elevation of 6 weeks' duration, of sleepless nights, chills and sweating on several occasions. This man was manager of several farms and was frequently thrown in contact with the dairy herds. Physical examination was irrelevant. Agglutination for *Br. abortus* was positive in a titer of 1 to 1280. Before a diagnosis of undulant fever had been established, this patient was given 10 cc. of 1% mercurochrome intravenously and later 3 cc. of sterile skimmed milk intramuscularly. Following each injection he showed a rather sharp thermal rise but no lasting improvement. On the 10th day after admission he was given the first treatment of 0.05 cc. typhoid mixed vaccine intravenously (see temperature chart for reaction). Treatment was repeated, convalescence was uneventful and check-up examination February 5, 1936, showed a normal individual whose blood gave a negative agglutination for *Br. abortus*.

CASE 3.—A. R., white male, aged 62, entered this hospital May 29, 1931, with the chief complaint of weakness and "stomach trouble." Well until 6 weeks prior to admission when the symptoms of weakness and fever were first noticed. Weakness was progressive. A diagnosis of undulant fever had been established by his family physician. Agglutination for *Br. abortus* was positive in a titer of 1 to 1280. Physical examination was irrelevant. Temperature fluctuated between 99° and 102°. He was given the first intravenous injection of typhoid mixed vaccine June 1, 1931, the second injection on June 6, the third on June 9, and following the last injection, temperature dropped to normal and remained so. He was discharged from the hospital June 29, 1931, symptom free. Check-up examination February 18, 1936, showed a healthy individual whose blood gave a negative agglutination for *Br. abortus*.

CASE 4.—L. G. K., white male, aged 54, entered this hospital January 22, 1930, complaining of weight loss amounting to 25 pounds and nervousness of 3 months' duration. Physical examination showed a warm, perspiring skin, moderate degree of emaciation, weakness and tremor of the muscles of the upper extremities and temperature which varied between 99° and 101°. Agglutination for *Br. abortus* was positive in a titer of 1 to 1280. Two weeks after admission the patient had his first injection of 250 million typhoid organisms intravenously. The temperature immediately started to "flatten out" and remained normal after the third injection. Improvement was phenomenal. He was discharged from the hospital February 12, 1930. Follow-up examination November 2, 1935, showed the patient to be in perfect health and agglutination to *Br. abortus* negative.

CASE 5.—J. M., white male, aged 38, entered this hospital December 1, 1934, complaining of pain in the abdomen and chest, chills and fever at night of 2 weeks' duration. For 12 consecutive days he had a daily, hard, shaking chill followed by high fever with diffuse perspiration. Malaria was suspected. Physical examination was remarkably negative. Blood agglutination was positive for *Br. abortus* 1 to 40 on December 7, 1 to 80 on December 13, and 1 to 320 on January 4, 1935. He was given routine treatment of 0.05 cc. typhoid mixed vaccine intravenously and his temperature returned to normal after the second injection where it remained. He was discharged from the hospital December 28, 1934. Check-up examination July 31, 1935, showed a normal individual except for subjective pain in the right knee joint. Blood gave a negative reaction to *Br. abortus*.

CASE 6.—A. D., white male, aged 14, entered this hospital May 14, 1933, complaining of fever of 4 months' duration. Symptoms began as headache

and fever. Onset was abrupt and he was confined to bed for several days. He improved so he could be up and around but continued to have afternoon chills, fever and headache. His temperature often went to 104°. During the 4 months of illness the clinical course was characterized by periods of exacerbation and relief. His temperature after admission fluctuated from around 100° in the morning to 105° in the afternoon. He had a chill followed by high fever every afternoon for the first week after admission. On the 8th day, treatment was instituted when he received 0.06 cc. typhoid mixed vaccine intravenously. This patient was given 6 injections of typhoid mixed vaccine and some improvement followed each treatment but temperature did not return to normal until after the last injection. He was discharged from the hospital June 3, 1933, much improved. Further convalescence at home was uneventful. Follow-up examination January 7, 1936, revealed a normal boy whose blood gave a negative agglutination to *Br. abortus*.

CASE 7.—H. B., white male, aged 50, entered this hospital April 17, 1935, complaining of chills and fever. Illness dated back to March 24, 1935, when he had his first chill followed by fever. Since that time he has had daily elevations of temperature. Agglutination for *Br. abortus* was positive in a titer of 1 to 320. Admitted to the hospital for typhoid vaccine therapy. His temperature returned to normal after the third injection. He had 0.05 cc., 0.075 cc. and 0.075 cc. typhoid mixed vaccine intravenously. His temperature dropped to normal and remained so. He was discharged from the hospital April 29, 1935. Agglutination for *Br. abortus* February 24, 1936, was positive but the patient has remained symptom free.

CASE 8.—G. H., white male, aged 32, was admitted to this hospital September 18, 1933, complaining of afternoon fever of 5 weeks' duration. Onset was acute with aching throughout entire body. Confined to bed for 2 days. Up and around afterward. Not able to work. Had non-productive cough since onset of illness, worse upon arising in the morning. Physical examination showed a well-nourished individual, not ill apparently. Agglutination for *Br. abortus* was positive in a titer of 1 to 640. His temperature ranged from 99° to 101°. He could not remain in the hospital so he returned home on September 19, but was readmitted September 25 for treatment. He was given 5 intravenous injections of 0.05 cc. typhoid mixed vaccine on the following dates: September 26, 28, 30, October 3 and 7. His temperature returned to normal after the third injection and remained normal thereafter except during treatment. He was discharged from the hospital finally October 10, 1933. He has been symptom free since. Agglutination was negative for *Br. abortus* August 26, 1935.

CASE 9.—W. H., white male, aged 53, entered this hospital from Devitt's Camp April 16, 1935. Diagnosed as acute undulant fever complicated by active pulmonary tuberculosis. Due to the fact that this patient was suffering from tuberculosis, he was given only 0.035 cc. mixed typhoid vaccine as a first dose and 0.025 cc. for the second, third and fourth. Temperature response was similar to those illustrated by Chart I. He was discharged from the hospital May 1, 1935. Follow-up January 28, 1936, reveals no symptoms referable to undulant fever but his agglutination for *Br. abortus* is still positive in a titer of 1 to 160. October 21, 1935 it was positive in a titer of 1 to 320.

CASE 10.—A. B., white male, aged 40, was admitted to Devitt's Camp June 18, 1934. At that time his temperature was fluctuating between 99° and 100°. He was treated by pneumothorax and as a result his temperature gradually declined with only occasional exacerbations, reaching normal October, 1934, where it remained until February 1, 1935. Another exacerbation of temperature began at this time which persisted until March 2 when it began to subside. On March 19, 1935, he entered this hospital.

His blood showed a positive agglutination for *Br. abortus* in dilution 1 to 1280. While here, his temperature continued to drop and when he left the hospital March 25, it was fluctuating between 98° and 99°. After returning to the Camp, his temperature remained practically normal. This is an example of a patient suffering from undulant fever and active pulmonary tuberculosis who made an uneventful recovery without any special therapy. It has been suggested that perhaps the tuberculosis had some influence in the favorable termination of the undulant fever. On January 28, 1936, an agglutination test of the blood serum for *Br. abortus* was negative.

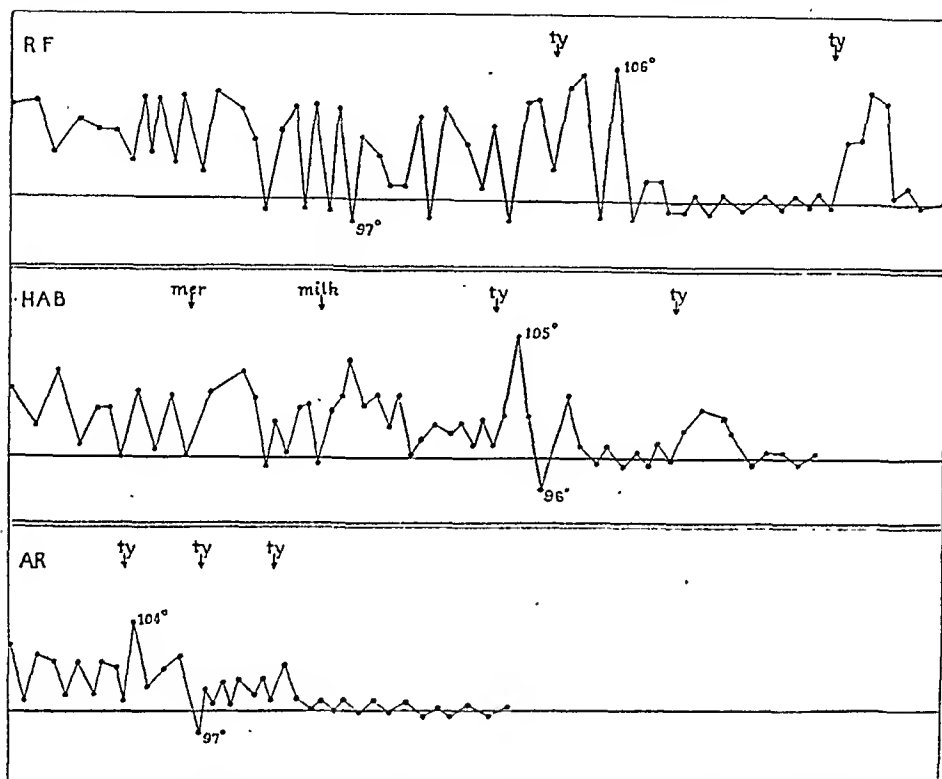


CHART I.—Fluctuations of temperature following the intravenous injection of killed typhoid and paratyphoid "A" and "B" bacilli. (Ty = injection of killed typhoid and paratyphoid organisms; Mer = mercuriochrome.)

CASE 11.—J. K., a white male, aged 19, entered this hospital January 18, 1930. This patient ran a typical course of undulant fever with onset of symptoms December 21, 1929. He had a normal morning temperature but afternoon temperature rose to 102° or more. While in the hospital, temperature fluctuated between 99° and 101.4°. When he was discharged from the hospital January 27, 1930, the fever was not improved. He went home and has had no special therapy. He continued to have fever for 5 months after he returned home and his physician reported 5 years later that he had never returned to his normal health. He still complains of periods of fatigue, vague, fleeting pains in various parts of his body, heart consciousness, but he has had no recurrence of fever. This patient was under observation before the use of typhoid vaccine had been instituted. His convalescence undoubtedly could have been greatly shortened by this agent.

CASE 12.—D. L. S., white female, aged 51, entered this hospital August 22, 1935, complaining of pain in the legs and joints, "poor heart," cough, repeated attacks of fever and night sweats of more than a year's duration. Ten months before admission she had been confined to bed for 4 weeks with fever of unknown origin. In January, 1935, she was admitted to another hospital where a diagnosis of undulant fever was made. She remained in the hospital for 30 days but her symptoms continued. Physical examination revealed a poorly nourished woman prematurely senile, sunken eyeballs, red tongue, pussy tonsils, heart sounds of poor quality, inguinal hernia, rectocele and cystocele, slight swelling of the hands, especially of the second metacarpal phalangeal joints. Our first impression was that the patient had a malignant disease masquerading under the diagnosis of undulant fever. Agglutination for *Br. abortus* was positive 1 to 320. Her temperature was of an irregular pattern reaching a peak of 101.4°. She was given 0.05 cc. typhoid mixed vaccine intravenously on the 13th day after admission. This dose was repeated twice. Improvement was rather phenomenal except for the fact that she has continued to complain of pain in the joints. After the first injection she had a desire to get out of bed and began to take an interest in things about the ward. She was discharged October 8, 1935. Follow-up examination January 10, 1936, showed an agglutination test for *Br. abortus* was positive in a titer of 1 to 60. She was greatly pleased with improvement made to date, however. She was unquestionably a case of chronic undulant fever and we are glad to include her in this series.

Discussion. It is of interest to conjecture as to the manner in which such a non-specific substance as mixed typhoid vaccine influences the course of undulant fever. One is impressed by the fact that almost any substance which will bring about a sharp thermal reaction will act favorably on the infection of undulant fever. For instance, Debono⁵ noted that after giving intravenously a filtrate prepared from Brucellin and Melitine that the temperature of the patient reached a maximum in 17 or 18 hours and then it came down the next day. He was able to bring the temperature down to normal after 2 or 3 injections of this material. It is noted in one of our cases, for instance, after the use of mercurochrome and skimmed milk, a favorable influence was exerted upon the fever. Our experience corresponds to the favorable results reported by Sinclair Miller.⁶

The mechanism of recovery is still a matter of speculation. In a previous article we reported that from the hemocytologic standpoint, the most significant changes which occurred following the intravenous injections of killed typhoid and paratyphoid bacilli were found in the total leukocyte count, the neutrophils, the metamyelocytes and the lymphocytes. These observations were made by obtaining a control count immediately preceding the injection of killed organisms. Following the injection of the killed typhoid and paratyphoid bacilli a complete blood count was made at hourly intervals for a period of 4 hours; 24 hours after the injection another complete blood count was taken. With few exceptions the blood counts were made by the same person and the differential counts in all instances were checked by one of us.

In the series of cases reported in this article a similar study was made of each patient's blood and in every instance following the injection of the killed organism a relative leukopenia occurred in the first hour followed by a return to the pre-injection level in the second hour. In the third and fourth hours there was a leukocytosis, followed by a drop to the pre-injection level after 24 hours. The neutrophil response closely paralleled the response of the total leukocytes. The metamyelocytes showed no initial increase but a steady increase during the first 4 hours.

The lymphocytes showed an increase in the first hour and a decrease in the following 3 hours. The postinjection 24-hour count revealed that the lymphocytes were near the pre-injection level.

All of the hemocytologic changes just described were transient as evidenced by the fact that at the end of 24 hours the findings were practically identical with the pre-injection observations.

While the observations reported in this study do not explain why the patients recovered, we do feel that inasmuch as they were infected with a specific organism (*Br. melitensis* or *Br. abortus*), the results obtained strengthen the theory that the injection of killed typhoid and paratyphoid bacilli stimulate a general non-specific immunogenic reaction. This reaction is reflected in the altered blood picture which indicates a response of the reticulo-endothelial system to the foreign proteins injected.

Such a response may in turn be the fundamental reaction which is responsible for the production of resistance or immunity. While we do not know exactly where antibodies are formed, our results suggest that the injection of killed typhoid and paratyphoid organisms is responsible for the production in the body of non-specific or specific antibodies of sufficient quality to enable the patient to overcome the disease. Of course, one cannot discuss immunity without considering the rôle played by the phagocytes in ridding the body of bacteria. In the problem dealt with in treating these patients, phagocytosis may have played an important part, but from the results obtained from animal experiments which we will report in a subsequent article, we are convinced that the production of antibodies is the factor responsible for the patient's recovery.

Conclusions. 1. Of 12 cases of undulant fever observed, 10 were treated by the intravenous administration of typhoid vaccine. The results in all 10 were satisfactory. There have been no recurrences and the follow-up agglutination tests for *Br. abortus* were negative in 9 of the 10 cases treated. Two follow-up agglutinations in control cases were also negative.

2. These results compare favorably with the treatment reported by other authors who have used specific substances prepared from *Br. abortus*.

3. The distinct advantages of typhoid vaccine are its availability in all localities and the simplicity with which it can be administered.

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NEPHRITIS IN GOUT.

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ARETÆUS, the Cappadocian, a contemporary of Galen, is given credit for first describing a scanty, deep yellow, cloudy urine during attacks of gout.² Thus, some seven centuries after the recognition of gout by Hippocrates, attention was directed to the kidneys. The red granular kidney of this disease has been commented upon and described through many centuries. Nephritis has been regarded as a common complication in gout, and there have been a number of isolated case reports in the literature, but statistics on the subject of kidney disease in gout, based on series of cases, are lacking.

The lesion in the kidney that has been described in gout is that of "interstitial nephritis" (nephrosclerosis or the arteriosclerotic kidney); in fact, "interstitial nephritis" has often been alluded to as the "gouty kidney." Rarely have uratic deposits in the kidney in sufficient amounts to produce renal impairment been encountered. Nephrolithiasis, long supposed to be a manifestation of gout, is now regarded as incidental. On account of the belief that albuminuria and decreased renal function are common in gout, the old question of impaired renal function as an etiologic factor in this disease is still a point of controversy. In only a few instances have pathologic studies shown normal kidneys in gout.

Vascular disease and hypertension are thought to be fairly common in gouty subjects,¹ but it must be remembered that the age period in which gout usually occurs is the one in which essential hypertension and arteriosclerosis are frequent. However, the literature suggests that nephritis is more common in this disease than is expected in non-gouty patients of a similar age. The origin of the nephritis has been assumed to be on a vascular basis.

In the course of another study on gout² we were struck with the

extremely high incidence of the additional diagnosis of chronic nephritis in the cases of gout in this hospital. In an analysis of these cases, which constitute the material for this study, we have attempted to determine an approximate incidence of nephritis in gout and to study the clinical and pathologic types of renal disease.

We have reviewed the records of 55 cases of true gout admitted to this hospital from 1913 to 1935. Any cases in which the diagnosis was somewhat questionable were not included. We wish to emphasize that the diagnosis of gout was quite conclusively established. Most of our cases were the ones in which certain fundamental studies in gout were made and published by Pratt,³ McClure,⁴ Folin, Berglund and Derick.⁵ Thirty-nine (71%) of the 55 cases had tophi containing sodium urate crystals, universally accepted as pathognomonic of gout; the others had an unmistakable history of podagra, accepted by the above observers. Inasmuch as patients with gout usually die from other causes, we have autopsy studies in but 4 cases, and, fortuitously for this review, all of them had nephritis.

Analysis of Cases. In this series of 55 cases, there were 51 males, and 4 females, (1 a negro). Among the males there were 2 Greeks, 1 negro and 1 Turk; the others were Anglo-Saxon. The average age for the series was 52.4 years, and most of the individuals had had gout for over 10 years. Hearty eating has always been associated with gout, but obesity did not seem to be any more common in these cases than in the general population between the ages of 40 and 60. However, nearly all of them had a history of alcoholism. Most of the cases were seen during an acute attack. There were no cases of leukemia to account for a high blood uric acid value, but there was 1 instance of polycythemia. One patient had had chronic lead poisoning. On a clinical basis the series has been divided into 2 groups, those with and those without nephritis.

Gout With Nephritis. Of the entire series of 55 cases, 17 (31%) had definite nephritis. The great majority of these individuals were thinner than those without demonstrable renal damage. Fourteen (82%) of these 17 had tophi and the average duration of gout for the group was 11 years. The evidence of nephritis consisted of persistent albuminuria and significant impairment of renal function, as shown by at least two of the following tests, phenol-sulphonaphthalein excretion, concentration tests, McClean urea index and azotemia (Table 1). In 5 patients the renal damage resulted in uremia and death. Decreased kidney function, due to obstruction in the lower urinary tract, was not a factor in any of the cases.

Albuminuria of moderate to marked degree was a constant finding in this group. Azotemia was present in the majority of the cases, the blood urea nitrogen ranging from 15 to 260 mg. per 100 cc. Hypertension was present in 13 of the 17 cases, an incidence considerably higher than in the non-nephritic group. The range

in blood pressure was from 110/65 to 240/140, with an average of 180/110. The blood uric acid in these cases was, for the most part, distinctly elevated.* Since the uric acid is usually elevated in chronic nephritis without gout, we have simply tabulated the uric acid values (Table 1), making no attempt to interpret them.

TABLE 1.—CASES OF GOUT WITH NEPHRITIS.

Case No.	Age.	Type of nephritis.	Albuminuria.*	Phenolsulphonephthalein, %.	Nitrogen retention, B.U.N.	Blood uric acid, mg. %.	Blood pressure.	Congestive heart failure.	Vascular disease
1	59	Arteriosclerotic	+++	...	67	...	110/65	0	Severe.
2†	40	Arteriosclerotic and glomerular	++++	30-5	60	6.8	220/130	Slight	Moderate.
3†	46	Vascular	++++	5	260	...	220/120	Slight	Severe.
4	62	Vascular	++++	25	21	5.6	170/120	Slight	Moderate.
5	43	Vascular	++++	24	27	5.6	180/110	0	Slight.
6	55	Vascular	++++	5	35	3.6	185/140	Slight	Severe.
7	58	Vascular	+++	12	35	3.3	140/70	0	Slight.
8	41	Vascular	++++	40	19	7.7	190/120	0	Moderate.
9†	61	Vascular	++++	12	100	8.0	225/140	Slight	Moderate.
10	35	Vascular	++++	30	41	8.3	220/140	0	Moderate.
11†	27	Chr. glomerular	++++	5	215	6.7	120/80	Slight	Slight.
12†	46	Vascular	++++	5	260	...	200/120	0	Severe.
13	38	Vascular	+++	40	15	4.7	155/100	0	Slight.
14	35	Vascular	+++	30	32	6.8	190/120	0	Slight.
15	57	Vascular	+++	30	35	6.4	150/90	Moderate	Slight.
16	43	Chr. glomerular	++++	25	56	...	240/140		
17	43	Vascular	+++	42	30	3.5	135/95	0	Slight.

* Albumin: +, slightest possible trace; ++, very slight trace; +++, slight trace; +++++, large trace.

† Died in Uremia. Phenolsulphonephthalein (I.M.), normal range, 45 to 65% in 2 hours.

The clinical type of nephritis in 15 of those 17 cases, as nearly as it could be determined, was vascular ("interstitial nephritis" or nephrosclerosis). The other 2 patients had chronic glomerular nephritis. Of the latter, 1 (Case 16) is most interesting in that, after a podagra history of 10 years' duration, he developed the nephrotic syndrome with rapid progression, within a year, to hypertension and renal failure. Death which occurred outside the hospital was due to uremia or to a cerebral vascular accident. The other patient was seen with subacute glomerular nephritis approximately 1 year before the onset of podagra (Case 11). He died in uremia 2 years later.

All of the cases in this group had clinical evidence of arteriosclerosis of moderate to marked degree. Retinal hemorrhages and white spots were present in at least 6 of the 17 cases. One patient

* There have been several modifications of the original Folin method of blood uric acid determination (1913), the range of normal changing with each improvement in technique. In addition, since the blood uric acid level alone does not make a diagnosis of gout, it is well not to interpret the figures too closely. To include the normal figures given in the various modified Folin tests carried out in this hospital, we have arbitrarily chosen 5 mg. per 100 cc. as the upper limit of normal blood uric acid.

had chronic lead poisoning, mentioned because of its possible etiologic association with both arteriosclerosis and gout.^{6,7}

As expected, with the nephritis and hypertension, the percentage of cases with congestive heart failure (41%) in this group was considerably higher than in those without nephritis. We were surprised to find that the average age of this group of patients with nephritis was 45, 10 years less than the average age of the patients without nephritis.

TABLE 2.—CASES OF GOUT WITHOUT NEPHRITIS.

Case No.	Age.	Albuminuria.*	Phenolsulphonphthalein, %.	Nitrogen retention, B.U.N.	Blood uric acid, mg. %.	Blood pressure.	Congestive heart failure.	Vascular disease.
1	48	0	130/90	0	0
2	66	++	80	19	5.0	165/95	0	Moderate.
3	50	++++	6.8	190/120	Moderate.	Slight.
4	35	0	35	...	4.8	165/105	0	0
5	53	++++	2.4	115/90	0	0
6	43	0	50	28	4.9	130/90	0	0
7	45	++++	45	165/90	0	0
8	39	0	40	18	5.5	140/70	0	0
9	65	0	50	25	5.5	150/80	0	Slight.
10†	44	+	55	...	5.9	150/90	Severe.	Slight.
11	47	0	50	13	4.5	115/90	0	Slight.
12	54	0	...	10	3.0	130/90	0	Slight.
13	41	0	50	...	? 5.0	100/50	0	0
14†	62	++++	8.0	200/120	Moderate.	Moderate.
15	48	++++	6.0	125/80	0	Moderate.
16	56	0	145/90	Slight.	Moderate.
17	53	0	120/60	0	Slight.
18	57	0	1.0	135/80	0	0
19†	55	+++	55	...	5.7	145/80	Moderate.	Moderate.
20	70	+	40	180/90	0	Moderate.
21	68	++++	180/90	0	Moderate.
22	70	0	5.7	160/90	Severe.	Severe.
23	40	0	4.0-5.0	135/70	0	Slight.
24	65	0	45	11	4.7	215/120	0	Slight.
25	54	0	47	13	3.6	135/70	0	0
26	70	+++	...	15	...	180/80	0	Moderate.
27	58	0	6.3	160/90	0	Slight.
28	69	0	5.2	135/80	0	0
29†	69	+++	45	11	4.6	120/70	Severe.	Severe.
30	47	+	...	15	3.5	135/95	0	Slight.
31	40	0	45	9	4.2	130/90	0	Slight.
32	53	0	45	10	5.8	110/70	0	0
33	41	++	50	15	3.9	125/90	0	0
34	64	++++	50	8	4.4	210/105	0	Moderate.
35	66	0	50	20	5.2	210/120	Slight.	Moderate.
36	62	+++	45	185/100	Slight.	Severe.
37	57	+	50	14	6.4	215/105	0	Slight.
38	61	++	...	15	...	150/60	Slight.	Slight.

* Albumin: +, slightest possible trace; ++, very slight trace; +++, slight trace; +++++, trace.

† Albuminuria associated with cardiac failure. Phenolsulphonphthalein (I.M.): normal range, 45 to 65% in 2 hours.

Gout Without Nephritis. The average age for this group was 55 years. There was a slightly greater incidence of obesity in this group than in the other, but it was not unusual for this age period. Twenty of the 38 patients (53%) had tophi, and the average duration of gout in this group was 13 years, 2 years longer than in the cases with nephritis. As seen in Table 2, 16 of the cases had albuminuria of slight to moderate degree, but no other findings on which

to make a clinical diagnosis of nephritis. The albuminuria was due to cardiac failure in 4. However, in another case of severe congestive heart failure (Case 22) albuminuria was not observed in many examinations. During an attack of gout, albumin in the urine has been considered rather common, but it could be possibly attributed to this cause in only 8 cases (21%), in which we could find no other explanation.

Kidney function, as investigated by the tests already enumerated for the cases with nephritis, was essentially normal for this group. It was only slightly impaired in a few instances, not enough in any case, however, to warrant a clinical diagnosis of nephritis.⁴ Although the uric acid excretion, before and after the use of various drugs, special diets and even the intravenous administration of uric acid was determined in most of the cases, we have considered it unnecessary to utilize these data, previously reported by others, as this would only lend further proof to the diagnosis of gout.

It has long been established that the blood uric acid need not be elevated even during an attack of gout. However, the blood uric acid was above 5 mg. per 100 cc. in 13 of the 38 cases of this group.

A comparison of the blood pressure in the two groups showed a striking difference. The average blood pressure was considerably lower in this non-nephritic group. Less than half—14—had hypertension (over 150 mm. Hg systolic and 95 mm. diastolic). In these 38 patients the blood pressure ranged from 100/50 to 215/120, averaging 165/90. As previously mentioned, these individuals showed considerably less arteriosclerosis, though they were 10 years older, and only 8 cases (21%) had congestive heart failure.

The fact that 16 cases with albuminuria and 14 with hypertension are included in a group of 38 cases under the heading "without nephritis" demands an added statement. The presence of albuminuria or hypertension alone does not make a diagnosis of nephritis. Although a significant degree of albuminuria and hypertension together was present in 6 of the 38 patients, as far as we were able to determine from the evidence available, there was no impairment of renal function to justify a diagnosis of nephritis in any of these cases.

Pathologic Anatomy. The pathologic descriptions of the kidney in gout in isolated cases in the literature for the most part have been those of chronic "interstitial" nephritis. The degree of contraction has been found to be so severe in some cases as to lead a few authors^{8,9} to describe this kidney as a "primary granular atrophy." Deposits of urates may occur in the interstitium of the kidney, usually in the medullary portion, best seen in the gross specimen, in addition to the interstitial nephritis. These deposits may be very extensive, as in a case recently described by Fahr,¹⁰ but a survey of the literature shows that such instances are not the

rule in gout. Such deposits have not been given primary consideration, though Fahr would seem to place more significance upon them than do other writers. It is Umber's opinion⁸ that "the urate deposits can exist in the gouty kidney without the manifestations of chronic nephritis, and they have in no way any serious connection with the renal disease." Many of the older clinicians supposed that the renal disease in gout predisposed to or caused kidney and bladder stones; we may presume that stones occurring coincidentally in a gouty patient might develop more rapidly, but nephrolithiasis is now supposed to have no necessary connection with gout, but to depend on bacterial and other local causes.¹ Finally, the most common form of uratic deposits in the kidney is the uric acid "infarct," composed of ammonium rather than sodium urate, occurring in infants. This condition has no association with gout.^{10, 11, 12}

We are indebted to Dr. S. B. Wolbach for reviewing with us the histopathology of the kidneys of our 4 necropsied cases, descriptions of which follow:

Pathology of 4 Cases. CASE 1.—(Table 1.) The right kidney weighed 55 gm.; the weight of the left was not recorded, nor histologic examination made. The capsules stripped easily from a moderately granular surface of lighter color than usual. The left kidney contained a cyst, 2.5 cm. in diameter; the parenchyma of the right kidney contained a few smaller cysts. Microscopically, the glomeruli were essentially normal except in areas of fibrosis corresponding to a few moderately sclerosed arcuate arteries. There was only slight intimal thickening of the smaller arteries. The tubules for the most part were normal. Leukocytic infiltration was absent. The slight histologic changes were those of arteriosclerosis in a kidney weighing only 55 gm. It was concluded that the right kidney was hypoplastic.

CASE 2.—(Table 1.) The right kidney weighed 105 and the left 30 gm. The left was an anomalous mass of fibrous tissue with small cysts containing clear fluid; the right, a typical red granular kidney with a small adenoma in the upper pole. On section the cortex measured 3 to 6 mm. and was scarred; the glomeruli were irregular and indistinct. In the medulla were streaks of white crystallin material (uric acid crystals), most numerous in the boundary zone. This gave a fan-shaped and striped appearance. Microscopic study showed extensive diffuse fibrosis with atrophy of the remaining renal elements. Generally the glomeruli showed marked fibrosis of varying degree, the majority being reduced to acellular hyalinized cicatrices. However, the changes in a few were suggestive of an old glomerular nephritis. The large arteries showed marked concentric thickening of the intima, proliferative in type, with marked diminution of the lumen. The small arteries and arterioles showed thickening of their walls with hyalin changes associated with hypertension. The tubules were dilated or atrophied and separated through interstitial fibrosis. The process was predominantly that of arterial and arteriolar nephrosclerosis, possibly superimposed upon a healed glomerular nephritis.

CASE 3.—(Table 1.) Each kidney weighed 55 gm. The capsule stripped without difficulty from a finely granular, pallid surface. The cortex was thin and scarred. The smaller arteries appeared sclerosed. Microscopic study showed concentric thickening of the intima, proliferative in type, of the large arteries. The small arteries and arterioles showed marked hyalin degeneration and thickening of the walls. The glomeruli were markedly

reduced in number, being represented mostly by hyalinized fibrous tissue incorporated in areas of diffuse fibrosis. A few appeared essentially normal and hypertrophied. Others showed old subcapsular adhesions. Many of the tubules were atrophic or replaced by fibrous tissue; others were hypertrophied and distorted. The pathologic picture was that of a healed glomerular nephritis followed by arterial and arteriolar sclerosis with additional glomerular damage.

CASE 4.—(Table 1.) The left kidney weighed 185 and the right 160 gm. The capsule stripped with difficulty from a slightly nodular surface in which there were deep, irregular scars. The bloodvessels were moderately sclerosed; the cortex was slightly thinned. Microscopically, there were surprisingly few changes. The arterioles were essentially normal. An occasional small and medium-sized artery showed intimal thickening and hyalin degeneration with slight fibrosis of the corresponding glomeruli. Otherwise the glomeruli were not remarkable. There was no increase of connective tissue; no leukocytic infiltration. A few of the tubules showed slight epithelial degeneration. The residual changes, then, were those of slight arteriosclerosis. Moderate arteriolar sclerosis, however, not seen in the kidneys, was seen in sections of the pancreas and adrenals.

Discussion. For many years after the work of Garrod in 1848,¹³ the theory that impaired renal function is the primary factor in the cause of gout largely dominated the viewpoint of both clinicians and pathologists. More recently, opponents to this theory^{8,14} have stated that functionally normal kidneys do occur in gout; pathologically, however, Moore¹⁵ found normal kidneys in only 6 of 80 cases.

Before the development of modern renal function tests, a diagnosis of kidney disease was made chiefly from the presence of albuminuria and cylindruria alone, and obviously any statistics on such a basis are erroneous. By such criteria over half of our 55 cases had nephritis, but with our present methods, actually only 31% had enough renal impairment, as shown by ordinary clinical tests, to be termed nephritis.

We have included with our cases of nephritis 2 of the patients shown by McClure⁴ to have, by more delicate tests, renal impairment, but insufficient at that time for a diagnosis of nephritis. However, further observation of these 2 cases has established a definite diagnosis of nephritis. Other cases reported in his series are included in our non-nephritic group. In his studies these showed only the slightest renal impairment; but unfortunately we do not have follow-up studies to determine if they too had nephritis. Contrary to McClure, we must conclude from the larger series now available for study, that impairment of renal function in gout, judged by the ordinary tests, is uncommon in the absence of nephritis. We also believe that albuminuria in gout, when not due to cardiac failure, is not as common as many have supposed in the absence of nephritis. This is in disagreement with Williamson,¹⁶ who found albuminuria in 45% of his cases but diagnosed nephritis in only 6%. In 8000 cases of gout which Gemmel¹⁷ claims to have observed, 10% had albuminuria and only 3 cases had definite evi-

dence of nephritis. These two are the only studies we have found in the literature, since the introduction of modern kidney function tests, giving an incidence of nephritis in gout. However, neither of these authors stated whether or not kidney function had been determined in their cases.

Associated with the supposed frequent occurrence of nephritis in gout, which has been regarded as "interstitial" or vascular in type, one would expect to find a large amount of generalized vascular disease as well as hypertension. However, the evidence in the literature on this point is contradictory. The viewpoint of the older writers is well expressed in an aphorism by Huchard,¹⁸ that "the gout is to the arteries as the rheumatism is to the heart." The more recent concepts are as given by Aschoff,¹⁹ that "genuine gout has nothing to do with arteriosclerosis," and by Allbutt,¹ that "regular gout and hypertension are not more than incidentally associated. . . . Arteriosclerosis, whether with high blood pressure or not, is a frequent but by no means obligatory concomitant of gout." From the high incidence of vascular disease (67%) and hypertension (54%) in our series we must agree with the opinion of the older clinicians. Mathieu, Colleson and Choltus²⁰ recently stressed the early development of vascular disease in gout.

For comparison, we have removed from our series the 3 known cases of glomerular nephritis in which the vascular disease and hypertension might be considered secondary to the renal disease and assumed that the remainder of the cases had at the beginning primary or essential hypertension simply occurring in a gouty subject, or even before the development of the gout in some cases. This showed a much higher incidence of vascular disease, hypertension and nephritis than in control groups of cases of similar ages. Furthermore, the incidence of the clinically manifested nephrosclerosis in these cases of gout is considerably greater than any control group of essential hypertension of similar ages.

Although data are not available regarding the percentage of clinical nephritis in essential hypertension, by the tests of renal function used in our cases of gout, the incidence would surely be much less than 25%. Fishberg²¹ believes that the most important criterion that clinically significant renal impairment is present or definitely impends in essential hypertension is the appearance of papilledema and that this occurs in less than 10% of the patients. Likewise, compared to the general population of this age period, the frequency of vascular disease and hypertension is much higher in our series of cases of gout. Although the incidence of arteriosclerosis in the general population is difficult to establish accurately, Sydenstricker's extensive statistical studies²² show clinical vascular disease in about 20 to 30% of individuals between 40 and 60 years. It is easier to determine the incidence of hypertension, and this, Alvarez and Stanley²³ found to be 12% in cross-section of the population in the same age period as our cases.

From the standpoint of nephritis alone, regardless of the type, everyone will agree that it does not occur in the non-gouty adult population in a per cent as high as we have observed in gouty patients (31%). Moreover, nephritis does not complicate other chronic diseases with any such frequency. For example, in chronic arthritis²⁴ and diabetes mellitus²⁵ nephritis is said to be of no greater frequency than in any group of normal individuals of the same age.* A high incidence has been given in pernicious anemia.^{26, 27} An impairment of renal function in this disease, however, does not necessarily indicate nephritis, since kidney function may improve with the subsidence of the severity of the anemia.²⁸ Furthermore, the most recent observations²⁹ have shown less than 5% clinical nephritis in patients with pernicious anemia, even though it was predicted that liver therapy would produce kidney disease.²⁷ To reiterate, Fishberg states²¹ that the complication of chronic arthritis, diabetes or pernicious anemia by "nephritis" is accidental.

In an attempt to explain the high incidence of vascular disease, hypertension and nephritis in our cases of gout, we have considered several of the more important factors believed to predispose to these conditions. Heredity is accepted as the most important, and it is the one stressed in most discussions of hypertension and of gout. Since only 2 of our cases gave a definite family history of gout, we agree with Williamson that the hereditary nature of true gout has been overemphasized. Garrod states³⁰ that there is an hereditary tendency toward "interstitial" nephritis in gout, but our observations do not substantiate this. There was a positive family history of vascular disease in 37% of our nephritis cases and 35% of those without nephritis. These figures are essentially the same found in control groups.^{31, 32, 33} Opposed to this, a family history of vascular disease has been reported in 65 to 75% of the cases of primary hypertension.³¹

Alcohol at one time was thought to be³⁶ an important factor in the production of vascular disease. Inasmuch as alcohol has always been regarded as a companion of gout, and as nearly all of our cases were moderate to heavy drinkers, we felt this should be mentioned. It can be dismissed quickly with the statement that there is sufficient evidence in the literature that the etiologic significance of alcohol in vascular disease seems to have been disproved. Recent studies^{34, 35, 36} have shown that alcohol in either small or large amounts plays no substantial part in the cause of arteriosclerosis, nor does it cause hypertension.²³ As a matter of fact, it has been Leary's observation that, as a class, persons suffering from alcoholism appear to show a lesser degree of atherosclerosis than their ages would justify.³⁷

* Since writing this paper, Joslin (*The Treatment of Diabetes Mellitus*, Philadelphia, Lea & Febiger, p. 164, 1935) has stated that the incidence of chronic vascular nephritis is somewhat higher in diabetic than in non-diabetic patients.

Obesity and diabetes mellitus are other factors included in most treatises on vascular disease and hypertension. There were no instances of diabetes in our series. Obesity, though it may not necessarily be a cause of high blood pressure, is a frequent concomitant of essential hypertension.³⁸ In the entire series there was no greater frequency of obesity than one finds in normal individuals of this age; however, the patients without nephritis showed slightly more obesity than the nephritic cases which had the more vascular disease. No one of the other numerous factors usually given in consideration of vascular disease and hypertension would account for the high incidence of these conditions in our cases. It seems, therefore, that we must attribute the unusual amount of vascular disease and increased blood pressure to some other factor, possibly to the gout itself.

With the exception of 2 cases of glomerular nephritis diagnosed clinically and another one diagnosed pathologically, the remainder of the cases of nephritis, as far as we could determine clinically, were of the vascular type. There was only 1 patient, a case of subacute glomerular nephritis, in which we were certain that the nephritis antedated the gout (Case 11, Table 1). In another patient the glomerular nephritis and nephrotic syndrome, which evidently developed years after the onset of podagra, was probably unrelated to his gout.

Pathologically, most of the various changes that have been described for the kidney in gout are represented by the 4 cases that came to necropsy. These were arterial and arteriolar sclerosis, with and without uratic deposits in the interstitium, chronic glomerular nephritis with the usual secondary vascular changes in the kidney and arteriosclerosis of the medium-sized arteries in the absence of significant changes in the arterioles. This last condition in 1 case was hardly more than one would expect in an individual of this age; however, clinically there was evidence of at least a moderate degree of nephritis. Although it seems necessary to consider some unknown factor to account for the high incidence of vascular disease and nephritis in our cases, it appears evident that clinically and pathologically the underlying lesion in the kidney was predominantly vascular. The glomerular nephritis does not seem related necessarily to the gout, and its occurrence was probably not greater than would be expected in any collection of cases of chronic nephritis in the broad sense.

Summary. In a study of 55 cases of true gout, 17 (31%) had clinical nephritis substantiated by commonly used tests for renal function. It was of the vascular type in 15 and glomerular in 2. One of the latter had the nephrotic syndrome. Five died in uremia. Of 4 cases necropsied, 3 had predominantly vascular nephritis and 1 had glomerular nephritis. The average age of the cases with nephritis was 10 years less than that of the non-nephritic group.

Of the remaining 38 cases without nephritis, 16 had albuminuria; in 4 of these it was definitely cardiac in origin. In this group renal function was very slightly impaired in 1 case and questionably so in 3, but not enough for a diagnosis of nephritis. Compared to certain control groups, the incidence of hypertension in the 55 cases (54%) and of vascular disease (67%) was high.

Conclusions. 1. An incidence of 31% of chronic nephritis in 55 cases of true gout is unusually high when compared to other chronic diseases, as essential hypertension, chronic arthritis, diabetes mellitus and pernicious anemia.

2. From our clinical and pathologic studies the type of nephritis in gout is predominantly vascular, although glomerular nephritis does occur, possibly unrelated to the gout. Assuming that in our cases the vascular disease was generalized, from some cause which we could not determine, it progressed into clinical nephritis at an earlier age and in greater frequency than occurs in non-gouty subjects with or without hypertension.

3. Vascular disease and hypertension are more frequent in patients with gout than in non-gouty individuals of the same age. Heredity, alcoholism and obesity appeared to play no part in the vascular disease or hypertension.

4. From our study of 38 gouty subjects without nephritis, contrary to the opinion of others, we believe that kidney function is rarely significantly impaired in the absence of nephritis. Albuminuria in gout, when unrelated to cardiac failure, is not as common as has been believed, 21% in our series, unless nephritis is present.

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LIPOID PNEUMONIA AND CONDITIONS THAT MAY FAVOR ITS OCCURRENCE.

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IN the past few years several reports of so-called "lipoid" or "oil aspiration" pneumonia have appeared, chiefly in American pediatric and pathologic literature. It has previously been pointed out that a localized, proliferative and relatively benign type of pulmonary consolidation associated with the aspiration of lipid material was sufficiently distinctive to be recognized as a pathologic entity; only, however, since Laughlen's¹ observations has the condition been diagnosed clinically. As the experimental and clinical studies leading to its establishment as an entity have been adequately discussed by Pinkerton,² Goodwin,³ and Ikeda,⁴ review of other cases will not be included. The following 3 cases, all in children under 2 years of age, have been observed within the past 7 months on the service of the Children's Clinic of the New York Hospital.

Case Reports. CASE 1 (N. Y. H. 80963).—E. G., an 11-month-old male infant of Polish Hebrew parentage, was admitted to the hospital with the complaint of having had "phlegm on the chest" for 10 months and of never having developed normally. He had been put into a plaster cast within a few days after birth to correct a congenitally dislocated hip; for the first 2 months of life, therefore, he was practically immobile. The sequence of events during this period is not entirely clear but supposedly the baby developed a mild upper respiratory infection by the second week of life and from this he did not recover. By the fourth week he had a cough, constantly drooled large quantities of mucus which collected in the pharynx, vomited often and gained weight very slowly. He received either 20 drops of viosterol or 2 tablespoonfuls of cod liver oil daily, and, by the second month, in an effort to combat what seemed to be an almost continuous respiratory infection, he received albolene nose drops daily. The use of these drops was not discontinued until after hospitalization.

The child's condition remained relatively stationary for 7 months, that is, there was a more or less constant cough, accompanied by cyanosis during severe attacks, and associated with an excess amount of mucus in the throat. Vomiting was frequent, often nasal in type, with large amounts of mucus in the vomitus. He was subject to severe head colds about twice a month, episodes accompanied by fever and a profuse nasal discharge; from these he scarcely recovered before another infection supervened. During the summer months spent at the seashore he improved slightly and colds were less frequent following adenoidectomy in September, 1934. At this time the only Roentgen ray which was taken during his 10 months of illness was secured. It has been impossible to locate the film but the parents were told that he had "congested lungs" and an enlarged thymus; the child received Roentgen ray treatments for the latter condition. The infant had never been able to hold his head up or to sit alone. He did not talk. He recognized his parents and they felt that he also responded to external stimuli, such as the radio, but he had never played actively with toys. Dentition had been normal.

Physical examination in the Outpatient Department 10 days before hospital admission revealed mucus in the upper respiratory passages and increased tactile fremitus at both bases, but there were no changes in percussion note or adventitious sounds in the chest. In the 3 days before admission he developed a fever, vomited repeatedly, and seemed very weak. He was at this time thin, pale and listless, an infant who, despite his 10 months, looked no more than 3 months of age. Body measurements confirmed the impression of a marked physical underdevelopment. Due to the physical retardation it was difficult to evaluate the mental status. He grasped for objects if interested, recognized his parents, responded at times to spoken commands. He cried very feebly and made almost no voluntary movements, the extremities lying flaccidly wherever they were put. On admission his temperature was 37.8° C., respirations, 45, and pulse rate, 140. He presented the signs of a bilateral acute catarrhal otitis media and mild rhinopharyngitis. The mouth was held open most of the time, an excessive amount of saliva running out over the chin and almost completely obscuring the view of the pharynx. The gag reflex was very sluggish. Examination of the lungs revealed an impairment of the percussion note on the right, anteriorly over the upper lobe, in the axilla and over the interscapular region. Breath sounds were very harsh throughout so that a superimposed pulmonary infection was postulated. The liver was palpable at the costal margin. Upon neurologic examination the reflexes were sluggish; marked hypotonicity of all tendons and musculature was present. There was a slight enlargement of lymph nodes (posterior cervical axillary and inguinal). There was no clubbing of the fingers and no other abnormalities. The red

blood cell count was 4,190,000 cells per c.mm.; white cell count 10,000 of which 42% were adult neutrophils, 15% immature, 38% lymphocytes, 2% monocytes and 3% eosinophils. A Mantoux test with 1 mg. of tuberculin was negative. Smear from the throat revealed many streptococci and staphylococci and *M. catarrhalis*, beta hemolytic streptococci, and *B. coli* communior were grown in culture. Repeated blood cultures were sterile and examinations showed the typical picture of a lipoid pneumonia on the blood. Roentgenograms revealed no abnormalities in chemical constituents of the as emphasized by Goodwin³ with a superimposed bronchopneumonia on the left. The densities in the right hilar field remained unchanged during his illness, the other shadows changing at each examination.

Three days after admission the child's temperature rose to 39° C., and his respirations to about 60, the signs of a pneumonic process became more prominent, and a purulent otitis media, staphylococci in origin, developed on the left. After the ninth day he was markedly worse; temperature varying from 39° to 41° C., the number of white blood cells falling steadily, pulse ranging from 130 to 180 and of very poor quality, the signs of consolidation increasing. Despite repeated transfusions, oxygen, and the usual cardiac stimulants, the child died 14 days after entry to the hospital, being practically moribund for the last 72 hours.

Autopsy (No. 7949). (Dr. Angevine, 2 hours after death.) The subject was poorly developed. The lungs were a mottled yellow-brown color except over the posterior part where there was considerable congestion. The pleura over the right upper lobe was thick, and firmly adherent to the parietal pleura. The right upper lobe was firm and cut with increased resistance. The remaining lobes of both lungs were firm and subcrepitant throughout because of the firm yellow-brown nodular areas that measured up to 5 mm. The cut surface was greasy and droplets adhered to the knife; they stained red with Sudan III. Small beads of purulent exudate were expressed from the terminal bronchi. The bronchial lymph nodes were enlarged about twice the normal size. The cut surface was a yellow-gray color and had the appearance of fat.

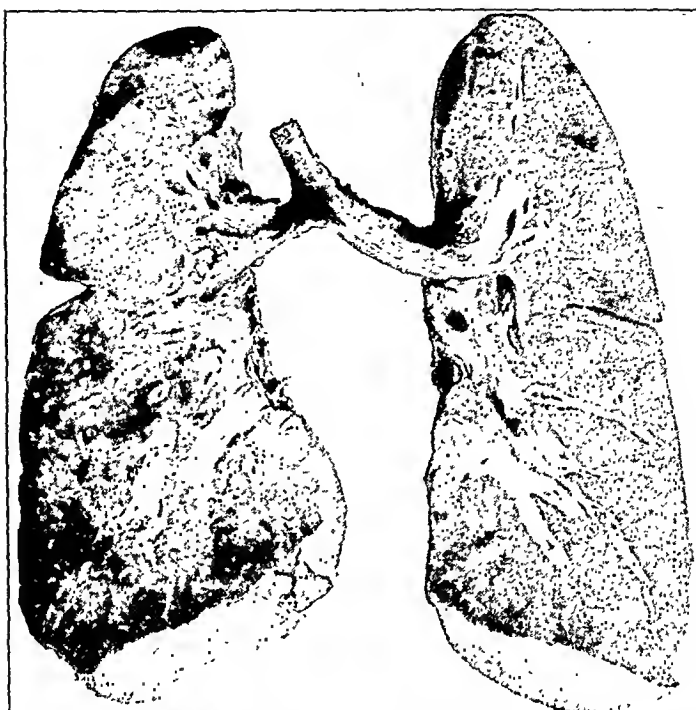
Microscopic Description of Lungs. A section through most of the right lung (Fig. 2) shows a lobular pneumonia with discrete nodules at the periphery of the lung becoming more confluent toward the hilus. Under higher magnification there are many large mononuclear cells containing fat droplets; they occur in groups with a lobular distribution and are associated with an increase of fibrous connective tissue. A cuboidal type of epithelium (Fig. 3) lines the alveoli and in many areas there is an acute inflammatory lesion composed largely of neutrophils. There are numerous large multinucleated giant cells (Fig. 5) containing fat droplets in the cytoplasm, and in several alveoli there are clumps of irregularly shaped masses of bluish staining material. Adjacent lymph nodes also contain many large mononuclear fat laden cells. In a frozen section stained for fat, most of the large one-fourth of the fat stains selectively with osmic acid.

Bacteriology. Pfeiffer bacilli were recovered from the heart blood; Pfeiffer bacilli and a non-hemolytic streptococcus from the lung.

Anatomic Diagnosis. Lipoid pneumonia of both lungs with consolidation of the right upper lobe; Zenker's degeneration of skeletal muscle; atrophic thymus.

CASE 2 (N. Y. H. 88565).—The child was a colored infant born prematurely in the seventh month of pregnancy. Birth history was unremarkable and there were no neonatal disturbances. At the age of 4 months he had rickets and 1 to 3 teaspoons of cod liver oil were administered from this time until hospital admission at the age of 8 months. The child had never sat alone, had had frequent spasmodic attacks of muscular twitchings

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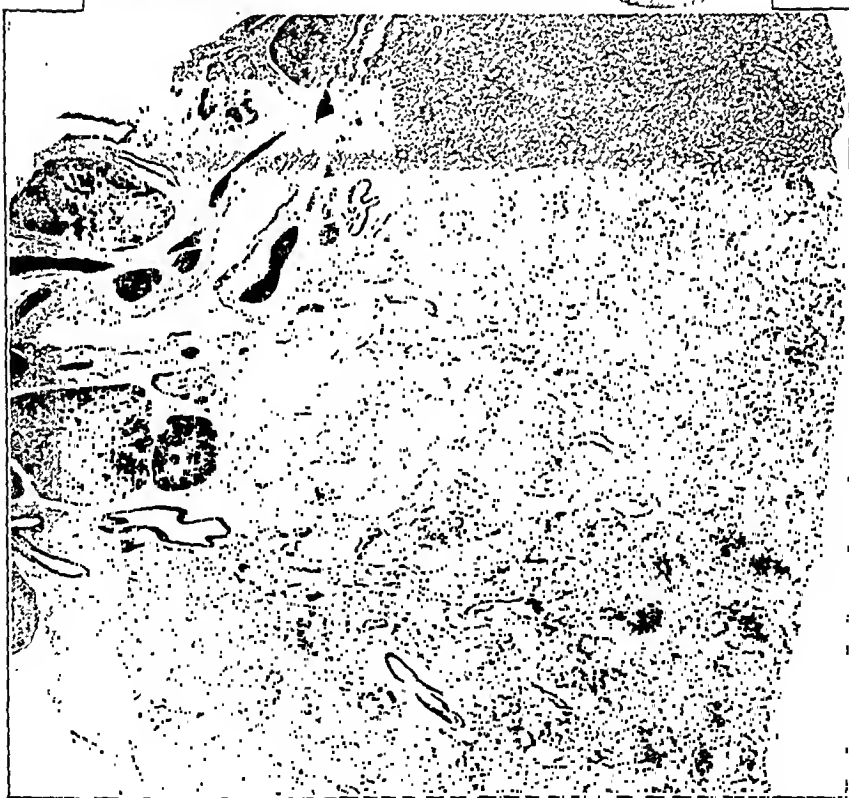


FIG. 1.—Autopsy 8035. A median section of the posterior halves of both lungs. The lipoid pneumonia involves the upper and a part of the lower lobe of the right lung.

FIG. 2.—Autopsy 7949. A section of the left lung to show the diffuse and nodular bronchopneumonia. Note the enlarged peribronchial lymph nodes. ($\times 4$.)



FIG. 3.—Autopsy 7949. A section to show the cuboidal epithelium lining the alveoli, the increase in fibrous connective tissue and the large numbers of neutrophils. ($\times 180$.)

FIG. 4.—Autopsy 8171. Frozen section stained with Sudan III. The black droplets represent mineral oil. ($\times 150$.)

FIG. 5.—Autopsy 7949. To illustrate large foreign body giant cells containing oil droplets. ($\times 390$.)

and movements of the extremities and he had never been a "bright baby." Dentition had been normal. His terminal illness began 3 days before admission when he had a fever, refused to eat, had been restless and finally developed labored respirations and vomited.

Upon admission the child was acutely ill, semicomatose, with a fever of 41° C., respirations 38, pulse 120. He was extremely well developed, but poorly nourished. Rachitic stigmata were present in the head and chest. There was definite evidence both on physical examination and by fluoroscopy of a pneumonic process in the upper lobe of the right lung, but this was not verified by any marked area of consolidation in the Roentgen ray films taken the next day. He had an acute pharyngitis and a bilateral catarrhal otitis media. The spleen and liver were enlarged and there was a small umbilical hernia. Interest was focussed chiefly upon the neurologic findings, for, in addition to a tense and bulging anterior fontanelle, he had a markedly stiff neck and a positive Brudzinski. All deep reflexes were hyperactive. Babinski, Oppenheimer, Gordon, Chvostek responses were negative. He was subject to intermittent spells of purposeless movements of the upper extremities, facial grimacing and twitchings. The arms were often thrown out violently with the hands, at times, in typical carpopedal spasms. Movements in the lower limbs were much less marked, though definite spasms were observed in small muscle groups. The hypertrophy of the skeletal muscles in the limbs gave the child the appearance of a miniature professional wrestler, the clinical picture simulating that described recently by de Lange.⁵ The head was held, for the most part, sharply turned to the right. Positive Brudzinski and Babinski signs were later elicited inconstantly; the neck and labyrinthine reflexes of Magnus and de Kleyne, spasticity and clonus in the lower jaw, also being observed. The pharyngeal reflex was not very active. Eye grounds were normal. Lumbar tap released a clear fluid under no increase of pressure. The child did very poorly, his temperature and respiratory rate increasing steadily, and he died 54 hours after admission. There were no unusual findings in the laboratory studies.

Autopsy (No. 8035). (Dr. Angevine, 35 hours after death.) The subject was a well developed male infant that weighed 6500 gm. The findings of greatest interest were those in the brain and lungs.

There was a thickening of the pia arachnoid, especially in the interpeduncular region. The walls of the internal carotid arteries were slightly thickened and there was a moderate degree of internal hydrocephalus. The choroid plexus in both lateral ventricles was somewhat atrophic. The third ventricle, aqueduct of Sylvius and the fourth ventricle were all slightly dilated. The optic thalamus on both sides was atrophic. Sections from the brain and spinal cord show a definite thickening of the meninges with an increase of fibrous connective tissue but few cells, mostly lymphocytes.

The lungs were salmon pink in color except over the posterior parts where they were congested. The right upper lobe was firm and through the pleura several small yellow lobular areas that measured up to 3 mm. were seen. The cut surface (Fig. 1) showed almost the entire upper and a small part of the lower lobe to be yellow-gray in color; the larger lobular areas were for the most part confluent except toward the periphery where they were circumscribed. A definite and unmistakable odor of fish oil was readily detected. The lymph nodes were slightly enlarged.

Microscopic Description of Lungs. In a section from the upper lobe of the right lung stained with hematoxylin-eosin there is a rather diffuse exudate composed largely of neutrophils together with mononuclears and erythrocytes. There is a slight increase in fibrous connective tissue and a few large multinucleated giant cells containing clear droplets. The bronchial epithelium is hyperplastic in one area. There are numerous large empty spaces, previously occupied by fat droplets. The alveoli are lined by a cuboidal epithelium in several places. In a frozen section many large

droplets take the Sudan III stain. In addition there are many cells containing small discrete orange stained droplets in the cytoplasm. In an osmic acid preparation there is about an equal amount of black staining material varying considerably in size and shape.

Anatomic Diagnosis.—Lipoid pneumonia of right lung; internal hydrocephalus; hemorrhagic pachymeningitis externa; Zenker's degeneration of skeletal muscle.

CASE 3 (N. Y. H. 79114).—A Jewish infant, 19 months of age, had developed normally up to the age of 6 months, after which she began slowly to degenerate mentally with a progressive hyperacusis, lethargy, and failure to note objects. There was no familial story of degenerative disease nor had the patient previously been ill. Her course was that of the typical case of amaurotic family idiocy, complicated 6 months before death by fever attributable to erysipelas, pyelitis, stomatitis and an upper respiratory infection. The pyelitis and stomatitis cleared rapidly but the skin infection was fairly prolonged. During the 10 months of her illness no symptoms of pulmonary disease were noted until about 6 months before death. There was then an area of dullness to percussion in the interscapular region, more marked on the right than on the left, and not varying markedly between examinations. There was also an increase in the intensity of the breath sounds in this region with an occasional râle. She ran an irregular fever during the last few months of life. A diagnosis of lipoid pneumonia was made and confirmed by repeated fluoroscopic examinations. She had been given 15 cc. of mineral oil and 10 drops of viosterol during most of the time she was in the hospital, and there was considerable difficulty in feeding her. Convulsive seizures were intermittent for many months before her death.

Autopsy (No. 8171). (Dr. R. J. Parsons; 2 hours after death.) The brain was large, heavy and firm; it weighed 1660 gm. The convolutions were larger than normal. The entire cerebellum, the pons and optic nerves were atrophic and small in comparison to the large hemispheres. The gray matter of the basal ganglia and cortex was unusually pale and firm. Sections from several areas of the brain and spinal cord are very similar. The nerve cells are much enlarged, rounded, vacuolated, and the Nissl substance is finely broken up. Material stained with Sudan III shows many large phagocytic cells filled with sudanophilic material.

Both lungs were of normal size. There were many definite discrete or confluent yellow nodules over the posterior half of the right lung that measured up to 1 cm. They were most conspicuous over the upper lobe and toward the hilus. On the cut surface these nodules were rather bright yellow in color, firm and slightly elevated above the surrounding normal lung tissue. The bronchial lymph nodes were enlarged to about twice their usual size.

Microscopic Description of Lungs. In many areas there is a quite definite fibrous thickening of the interalveolar septa with obliteration of the alveolar structure. Many alveoli are completely, and others partially, filled with large mononuclear phagocytes, the cytoplasm of which is filled with large clear vacuoles. A few neutrophils are seen in the capillaries of the interalveolar septa and a small number are free in the alveolar spaces. A Sudan III preparation (Fig. 4) shows abundant sudanophilic material varying from small intracellular droplets to large globules and amorphous masses that fill entire alveoli. An osmic preparation shows only one small free globule that stains black.

Other findings were an increase of fat in the lymphoid follicles of the spleen, about the central vein and in the Kupffer cells of the liver.

Bacteriology. Hemolytic staphylococcus aureus, non-hemolytic streptococcus and Bacillus coli communis were recovered from the lung.

Anatomic Diagnosis. Gliosis of brain and spinal cord (Tay-Sachs disease); lipoid pneumonia.

Summary. Three cases of lipoid pneumonia in infants under 2 years of age are described. Two occurred in children with extensive pathologic lesions of the central nervous system and one in a debilitated child who was restrained in a plaster cast because of a congenital dislocation of the hip. Clinical diagnoses were made in 2 instances on the basis of history with the physical findings and characteristic roentgenologic picture described by Goodwin.³ In 2 cases the cause was apparently the administration of mineral oil together with viosterol. The other case was due to codliver oil alone.

The fresh lungs all presented a somewhat similar and characteristic picture except for the amount of lung involved. They all showed yellow-brown, rather firm nodules readily seen through the pleura. The right lung and especially the upper lobe was most extensively involved in each instance. The diagnosis was made on the gross specimen in all cases and additional confirmatory evidence was obtained by the microscopic examination of scrapings from the fresh cut surface of the lungs for fat droplets. In 1 instance the sense of smell was of great aid. Microscopically the 3 cases showed a somewhat similar process, consisting of varying degrees of fibrosis and an infiltration into the alveoli of large mononuclear leukocytes filled with fat; in addition to this in 2 instances there was acute bronchopneumonia. In 2 cases cuboidal epithelium lining the alveoli was conspicuous and numerous large multinucleated foreign body giant cells containing fat droplets were present. Although the diagnosis can be readily made with an hematoxylin and eosin stain, it is highly desirable to make Sudan III and osmic acid preparation as an aid in determining the nature of the aspirated fat.

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THE INTRANASAL APPLICATION OF INSULIN, EXPERIMENTAL AND CLINICAL EXPERIENCES.*

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SINCE the discovery of insulin investigators have attempted to introduce it into the body by various methods. Woodyatt,¹ in

* This article forms a basis of an address before the American Clinical and Climatological Association, Princeton, New Jersey, October 21, 1935.

1922, says, "Experiments were conducted with oral, rectal, vaginal, intranasal, intravenous, and subcutaneous administrations. Inunctions were also tried. Many variations were attempted in connection with each. Positive effects were obtained with subcutaneous and intravenous injections, very weak, doubtful or frankly negative results with the others." Up to the present time intravenous and subcutaneous administrations have been employed to the exclusion of all other methods.

Telfer,² in 1923, reported that insulin could be introduced into the blood stream by means of inunction. Harrison,³ in 1926, repeated this work and found that the inunction of insulin was useless even in very large doses. Peskind, Rogoff and Stewart,⁴ in 1924, found that insulin when injected per rectum into rabbits was absorbed and produced lowering of the blood sugar; in dogs, negative results were obtained. Heubner, de Jongh and Laquer,⁵ in 1924, describe the lowering of blood sugar in diabetics by inhalation of insulin. Fisher,⁶ in 1924, found some absorption of insulin by the intestine, vagina and serotal sac. Gänsslen,⁷ in 1925, described lowering of the blood sugar in diabetics by inhalation of an insulin spray. Miller,⁸ in 1926, reported that insulin given in absolute alcohol or 95 per cent alcohol solution in keratinized capsules, lowered the blood sugar of diabetic patients. Stephan,⁹ in 1929, described lowering of blood sugar following the administration of insulin by mouth. This work was not confirmed by Wahneau and Bertram¹⁰ or by Bertram, Horwitz and Wahneau.¹¹ Bollman and Mann,¹² working with intestinal catheters and with ileae loops, found that large amounts of insulin might be instilled into the duodenum, jejunum, or ileum without any appreciable effect on the blood sugar of normal dogs. Similar results were found with administration into the ileac loop.

A summary of these results bears out the initial statement of Woodyatt that with methods other than subcutaneous or intravenous injection "very weak, doubtful or frankly negative results" have been obtained.

Recently we have repeated some of these experiments with variations, and in the course of our work, studied the problem of intranasal absorption. We have obtained undoubted evidence of the activity of insulin, either when sprayed or when instilled into the nostrils in normal rabbits, normal dogs and in diabetic patients under certain conditions.

The preliminary experiments indicated that the instillation or insufflation of insulin in the nose produced either frankly negative or doubtful results. We studied next various solutions which might possibly increase absorption through the mucous membrane. Finding several solutions which apparently had this effect, we chose first ethylene glycol as a medium. We have mixed equal quantities of ethylene glycol and insulin, using a highly concentrated solution

of insulin containing 1000 units per cc. The solutions employed for instillation contained 500 units per cc. With such a solution 0.1 cc. contains 50 units and 0.2 cc., 100 units of insulin.

The following are a few typical protocols on rabbits and dogs:

Date, 1935.	Animal.	Time.	Blood sugar, mg.
Mar. 13	Rabbit No. 1	8.50 A.M.	247.0
		8.55 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
		10.28 A.M.	177.0
		11.47 A.M.	149.0
Mar. 15	Rabbit No. 2	9.05 A.M.	105.5
		9.08 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
		10.40 A.M.	62.5
		12.40 A.M.	55.2
Mar. 20	Dog	9.50 A.M.	96.0
		9.55 A.M.	0.4 cc. insulin-ethylene glycol mixture (200 units) intranasally.
		10.50 A.M.	58.8
		11.45 A.M.	58.3
		12.45 P.M.	44.2

The effects of this solution when applied intranasally in diabetic patients were next studied. All of the patients studied had been under observation in the diabetic clinic for varying periods of time. On the day when the test was carried out both breakfast and the morning dose of insulin were omitted. In a few instances the evening dose before the day of the test was also omitted. The results are seen in the following table:

Case Reports. CASE 1.—Female, aged 70, first seen, January 30, 1935, with a fasting blood sugar of 233 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 150, protein 60, fat 90. Insulin dosage in units, 20 - 5 - 20, a total of 45 units per day.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 18	7.30 A.M.	150
	8.15 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	9.15 A.M.	149
	10.15 A.M.	122
	11.15 A.M.	83
	12.15 P.M.	110

CASE 2.—(Same patient as Case 1.)

Date, 1935.	Time.	Blood sugar, mg.
Mar. 19	7.30 A.M.	135
	8.15 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	9.15 A.M.	87
	10.15 A.M.	94
	10.15 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	11.15 A.M.	69
	11.15 A.M.	Slight reaction.
	11.30 A.M.	More marked reaction.
	11.40 A.M.	Orange juice.
	12.15 P.M.	115

CASE 3.—Male, aged 23, first seen, October 30, 1933, with a fasting blood sugar of 571 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 100, protein 100, fat 150. Insulin dosage in units, 11 - 0 - 9, a total of 20 units per day.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 21	8.00 A.M.	225
	8.50 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally (spray).
	9.50 A.M.	197
	10.50 A.M.	172
	11.50 A.M.	148
	12.00 NOON	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally (spray).
	1.00 P.M.	137
	2.00 P.M.	116
	7.00 A.M.	189
	3.00 P.M.	242
Mar. 22		

CASE 4.—Female, aged 24, first seen, March 21, 1935, with a fasting blood sugar of 256 mg. per 100 cc. The patient had followed no strict diet and had taken no insulin regularly before test.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 21	8.00 A.M.	256
	8.50 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally (spray).
	9.50 A.M.	154
	10.50 A.M.	125
	11.50 A.M.	115
	7.00 A.M.	254
Mar. 22		

CASE 5.—Female, aged 64, first seen, March 28, 1935, with a fasting blood sugar of 217 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 75, protein 50, fat 75. Insulin dosage in units, 10 - 5 - 10, a total of 25 units per day.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 29	8.30 A.M.	188
	9.30 A.M.	180
	9.40 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	10.30 A.M.	144
	11.30 A.M.	142
Mar. 20	7.00 A.M.	167

CASE 6.—Female, aged 47, first seen, April 28, 1928, with a fasting blood sugar of 323 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 50, protein 75, fat 100. Insulin dosage in units, 25 - 15 - 20, a total of 60 units per day.

Date, 1935.	Time.	Blood sugar, mg.
Mar. 30	12.15 P.M.	158
	12.20 P.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	1.15 P.M.	106
	2.15 P.M.	65
	3.15 P.M.	66

CASE 7.—Male, aged 44, first seen, April 3, 1935, with a fasting blood sugar of 286 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 50, protein 100, fat 150. Insulin dosage in units, 10 - 0 - 10, a total of 20 units per day.

Date, 1935.	Time.	Blood sugar, mg.
April 3	10.45 A.M.	286
	10.50 A.M.	0.2 cc. insulin-ethylene glycol mixture (100 units) intranasally.
	11.45 A.M.	112
	12.45 P.M.	67
	1.45 P.M.	73
April 4	7.00 A.M.	132

We next made observations employing trimethylene glycol instead of ethylene glycol. These solutions were prepared so that 0.1 cc. of the solution contained 75 units. The pH of the solution employed was 2.5. These solutions were apparently more active than those made with ethylene glycol.

CASE 8.—Female, aged 75, first seen, October 11, 1934, with a fasting blood sugar of 322 mg. per 100 cc. The patient had followed no strict diet before the test. Insulin dosage in units, 14 - 0 - 12, a total of 26 units per day.

Date, 1935.	Time.	Blood sugar, mg.
June 24	Fasting	206
		25 units insulin in trimethylene glycol (0.05 cc.) intranasally.
	1st hour	157
	2d hour	146
	3d hour	132

CASE 9.—Male, aged 34, first seen, June 15, 1935, with a fasting blood sugar of 238 mg. per 100 cc. The patient had followed no strict diet and had taken no insulin regularly before the test.

Date, 1935.	Time.	Blood sugar, mg.
June 24	Fasting	203
		25 units insulin in trimethylene glycol (0.05 cc.) intranasally.
	1st hour	222
	2d hour	198
	3d hour	189

CASE 10.—Male, aged 54, first seen, May 1, 1935, with a fasting blood sugar of 335 mg. per 100 cc. At the time of the test the patient was on a diet of carbohydrate 150, protein 75, fat 100. Insulin dosage in units, 20 - 10 - 20, a total of 50 units per day.

Date, 1935.	Time.	Blood sugar, mg.
June 24	Fasting	310
		25 units insulin in trimethylene glycol (0.05 cc.) intranasally.
	1st hour	224
	2d hour	165
	3d hour	158

CASE 11.—Male, aged 66, first seen, June 26, 1935, with a fasting blood sugar of 213 mg. per 100 cc. At the time of the test the patient was on a

diet of carbohydrate 100, protein 75, fat 50. Insulin dosage in units, 15 - 10 - 15, a total of 40 units per day.

Date, 1935.	Time.	Blood sugar, mg.
July 14	Fasting	240
		25 units insulin in trimethylene glycol (0.05 cc.) intranasally.
	1st hour	184
	2d hour	156
	3d hour	184
July 15	7.00 A.M.	211

Discussion and Summary. The above tables, which are examples of a larger group of similar observations, show that insulin in ethylene glycol and in trimethylene glycol when either dropped or sprayed into the nasal mucous membrane produces an unquestioned and marked fall in blood sugar in normal rabbits, normal dogs, and in diabetic patients. The dosage employed by this intranasal method is considerably greater than that necessary in subcutaneous injection.

Two impressions that we gain may be of some interest: First, in patients who prove later to be mild diabetics, the blood sugar falls very rapidly following intranasal application even when the blood sugar values are very high. Our second impression is that it is relatively difficult to produce insulin shock. While it is not difficult to lower the blood sugar from a high value to a range of 140 to 160, it is more difficult to lower the blood sugar below this level.

We have treated 15 patients in the hospital over periods of time varying from 2 weeks to 2 months and have been able to keep them relatively sugar free by the intranasal method. Whether this method of administration is practical in the treatment of diabetic patients further observations alone can determine. The treatment may prove too expensive to be practical and we may also discover that the variations in absorption in different patients at different times are too great to make this method of administration either practical or desirable. The fact that insulin under certain conditions can be absorbed from mucous membranes may, however, be of more than academic interest. Obviously the insulin molecule is not too large to pass through the intact mucous membrane. The action of the solutions employed in increasing absorption is not understood beyond the statement that they increase permeability. At present we do not believe that these observations establish either the desirability or the reliability of intranasal administration. They do, however, prove that intranasal absorption is possible.

We are under obligations to Eli Lilly and Company for the insulin used in these observations.

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THE EFFECT OF GASTRIC JUICE, BILE, TRYPSIN AND PANCREATIN ON INSULIN: THE PREVENTION OF THE DIGESTION OF INSULIN WITH ALCOHOL.

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VARIOUS attempts to make the oral administration of insulin effective have been practically unsuccessful. The reasons for these failures have been obscure. However, it appears either that insulin is destroyed or inactivated by gastro-intestinal enzymes or that the intestinal mucosa is impermeable to insulin, possibly because of its high molecular weight, which Sjörgen and Svedberg¹ found to be 35,100.

The purpose of this study was to investigate why the oral administration of insulin appears to be ineffective by determining the effect of gastric juice, trypsin, pancreatin and bile on insulin and to attempt to protect insulin, especially with alcohol, from being digested by these enzymes. This paper reports the results obtained in 116 experiments.

That insulin is destroyed by pancreatic juice was determined by Banting and Best.² This observation was confirmed by Scott³ and by Dudley,⁴ who showed, in addition to the inactivation of insulin by trypsin, that pepsin produced the same destructive effect. That the intestinal mucosa is impervious to insulin was suggested by the work of Bollman and Mann.⁵

Nevertheless there have been some studies which suggested that insulin may be protected by various substances and absorbed from the alimentary tract. Fisher and Noble⁶ were able to recover insulin from the urine, when administered by mouth. Winter,⁷ Miller⁸ and Harrison⁹ gave insulin in alcohol orally and caused a reduction in the blood sugar. However, Blatherwick, Maxwell and Long¹⁰ could not confirm these results. Murlin and Hawley¹¹ obtained considerable absorption of insulin protected by blood serum when given by stomach tube to depancreatized dogs. Lasch and Brugel¹² caused a decrease in blood sugar in man and in animals giving insulin in saponin and normal saline. Hamburger¹³ found that insulin dissolved in Ringer's solution is absorbed from the frog's intestine. Walton and Bassett¹⁴ introduced insulin diluted with saline into the intestines of normal dogs with Thierry loops and produced typical hypoglycemia. Harned and Nash¹⁵ described a preparation of antitrypsin which, when added to insulin and introduced into the duodenum, resulted in a considerable drop in the blood sugar. Fisher and Scott¹⁶ observed no marked decrease in the physiologic activity of insulin after incubation at 37° C. with pepsin at pH 4. Jensen and Evans¹⁷ suggested that the inactivation of insulin is connected in some way with hydrolysis of the protein.

Material. The gastric juice which was used was obtained by aspirating the fasting or non-fasting contents from patients with peptic ulcer, carcinoma of the stomach, carcinoma of the esophagus, gastric neurosis, pernicious anemia, secondary anemia, avitaminosis, cardiac decompensation, chronic nephritis with uremia, diabetes mellitus, gall stones, hypertension, hyperthyroidism, syphilis and normal individuals. Commercial trypsin and pancreatin were used. Bile was obtained from patients during operation. Ordinarily Lilly's U-20 insulin was employed. The rabbits used in the tests weighed about 5 pounds.

Plan of Investigation. The method consisted in mixing from 1 to 10 cc. (usually 10 cc.) of gastric juice with 20 units of insulin and incubating for 1 hour at 37° C. In some experiments the mixtures were incubated for as short a period as 5 minutes. The amount of free and total acid in the gastric juice was determined in each specimen. The free acid varied from 0 to 80, and since the amount of acid appeared to have no relation to the results, the individual figures for the acid will not be given. When pancreatin and trypsin were tested about 5 gm. of each was mixed with water, and the same procedure followed as with gastric juice.

The mixtures were injected intramuscularly into rabbits, and blood samples were obtained from the ear veins before the injection and afterward in $\frac{1}{2}$, 1, 2, 3 or more hours. The blood sugar* was determined according to the micro method of Folin.¹⁸

The method of insulin extraction was as follows: Eight parts of 95% alcohol were added to 1 part of the insulin-gastric juice mixture, thoroughly mixed and centrifuged. Since 10 cc. of gastric juice were mixed usually with 1 cc. of U-20 insulin, it required 88 cc. of 95% alcohol for the extraction of insulin. The supernatant fluid was removed and evaporated down to 1 or 2 cc. or to dryness *in vacuo* at a temperature of not more than 37° C. This was made up with distilled water to a volume of 10 cc. and injected into rabbits.

* Miss Honora F. Carroll gave technical assistance.

Effect of Gastric Juice on Insulin. The effect of gastric juice on insulin was studied first. A typical example of the results of the blood sugar determinations obtained in the rabbits after the injection of the insulin-gastric juice mixture is given in Chart 1. The results were all much alike. After the injection there was no drop in the blood sugar level such as is seen when 20 units of insulin alone are injected. Instead, there was usually a rise in the blood sugar of 5 to 25 mg. usually in $\frac{1}{2}$ or 1 hour after the injection and then a drop to near the original blood sugar level during the 3 or 4-hour period of observation.

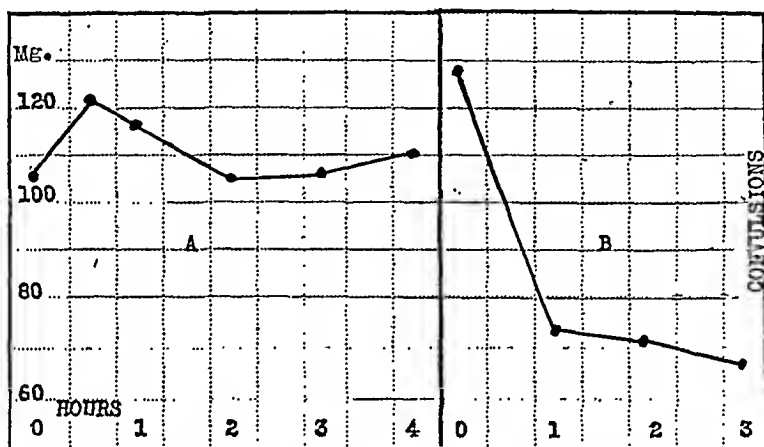


CHART 1.—Comparison of blood sugar curves obtained in a rabbit A, after the injection of 20 units of insulin incubated with gastric juice, and B, after the injection of 20 units of insulin in one leg and gastric juice in the other.

From these experiments it appeared that insulin was digested or inactivated by the gastric juice, even in the experiments where the insulin and gastric juice were incubated for as short a period as 5 minutes. In order to determine whether the insulin was simply inactivated, an effort was made to extract insulin from the incubated insulin-gastric juice mixture according to the method described.

The extract was injected and the blood sugar curves were observed for a period of 3 or 4 hours. The results obtained were much the same as those obtained following the injection of the incubated insulin-gastric juice mixture. This suggested that the insulin was digested, completely destroyed and could not be recovered.

Prevention of Insulin Digestion by Gastric Juice. The next step in this investigation consisted in trying to prevent insulin from being digested by gastric juice. At first an attempt was made to confirm the reported protective ability of blood serum, saline, Ringer's solution and saponin on insulin. Varying amounts of these substances were added to 20 units of insulin and incubated at 37° C. for 15 to 30 minutes. Then 10 cc. of gastric juice were added to each specimen, incubated for 1 hour and injected into rabbits. The

blood sugar curves showed no drop in the blood sugar level during the periods of observation. The results indicated quite clearly that blood serum, saline, Ringer's solution and saponin did not prevent gastric juice from destroying insulin.

It then seemed logical to try to protect insulin from digestion by dissolving or combining it with some chemical which is readily absorbed from the gastro-intestinal tract. Since insulin in alcoholic solution administered by mouth has been reported to cause a reduction in the blood sugar, alcohol was selected for this purpose. These experiments were conducted by dividing specimens of gastric juice into two equal parts of usually 10 cc. To one part, 20 units of insulin were added and incubated for 1 hour. This was injected into a rabbit, and the blood sugar curve was observed for 3 hours to serve as a control test. Then 20 units of insulin were dissolved in 10 cc. of 95% alcohol and incubated for 5 to 10 minutes. To this the second part of gastric juice was added and incubated for 1 hour. Since alcohol is irritating when injected, the insulin was extracted in the usual manner. This extract was injected, and the resultant blood sugar curves were determined.

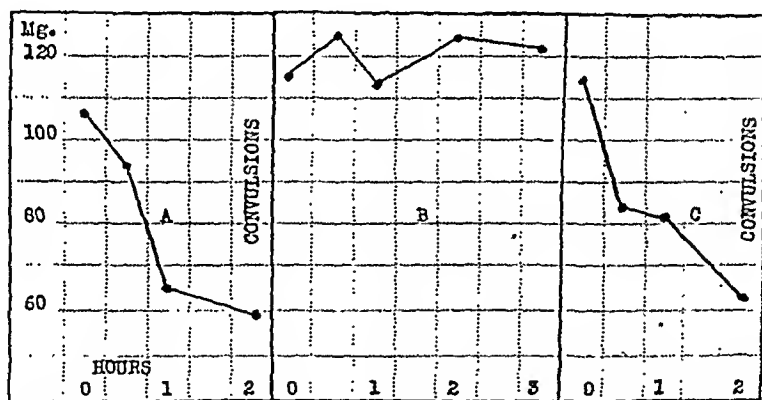


CHART 2.—Characteristic blood sugar curves obtained in a rabbit *A*, after the injection of an extract of 20 units of insulin dissolved in alcohol and incubated with gastric juice, *B*, after the injection of 20 units of insulin incubated with gastric juice, and *C*, after the injection of 20 units of insulin.

The results obtained were very striking and interesting. In the control tests the blood sugar concentration varied very little after the injection of the insulin-gastric juice mixture. However, the blood sugar curves following the injection of the extract from the mixture in which the insulin was protected with alcohol were quite different. A typical illustration of the results obtained is given in Chart 2. There was a marked reduction in the blood sugar level and the rabbits had convulsions usually in 2 hours and occasionally in 1 or 3 hours after the injection. The resultant blood sugar curves

were similar to those obtained when 20 units of insulin were injected. These results suggested that alcohol protected insulin from digestion by gastric juice, or that alcohol destroyed the enzymes in the gastric juice, thus preventing the digestion of insulin.

The experiments were repeated in an endeavor to protect insulin with varying quantities and concentrations of alcohol. The results obtained with as little as 5 cc. of 95% alcohol or 10 cc. of 48% alcohol were much the same as when 10 cc. of 95% alcohol were employed. However, when smaller amounts or concentrations of alcohol were used there was usually only a slight drop in the blood sugar level.

It was then ascertained whether alcohol destroyed the enzymes in the gastric juice. This was accomplished by mixing 10 cc. of 95% alcohol with 10 cc. of gastric juice and incubating for 1 hour. The alcohol was evaporated off *in vacuo*, and 20 units of insulin were added. This was incubated for 1 hour and injected.

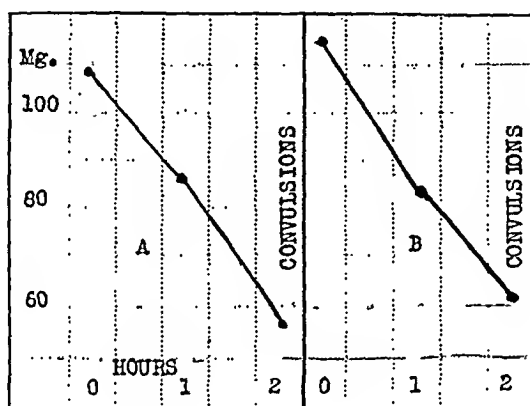


CHART 3.—Relative blood sugar curves obtained in a rabbit A, following the injection of 20 units of insulin incubated with gastric juice to which alcohol was added and evaporated off, and B, after the injection of 20 units of insulin.

The findings were all much the same as those noted when the alcohol was added first to the insulin. An illustration of the blood sugar curves obtained in the rabbits after the injection of this mixture is shown in Chart 3. These results suggested that alcohol destroyed the enzymes in the gastric juice and thus prevented the destruction of insulin.

It seemed important to learn whether alcohol entered into any chemical combination with insulin and thus prevented it from being digested. To study this aspect of the problem the experiments were repeated by adding 10 cc. of 95% alcohol to 20 units of insulin. This was incubated for 1 hour and evaporated to dryness *in vacuo*. Then 10 cc. of gastric juice were added and incubated for 1 hour. This was injected, and the blood sugar level was observed over a period of 3 to 5 hours.

The blood sugar curves obtained in these tests were not remark-

able. There was only a slight maximum reduction of 10 to 33 mg. in the blood sugar concentration in 2 or 3 hours after the injection, and in some experiments there was no decrease in the blood sugar. A typical example of the results is shown in Chart 4. Apparently insulin and alcohol did not enter into any combination to protect it from digestion after the evaporation of the alcohol.

The results in general suggested that alcohol protects insulin chiefly by inactivating the peptic enzymes and thereby preventing the gastric juice from destroying insulin.

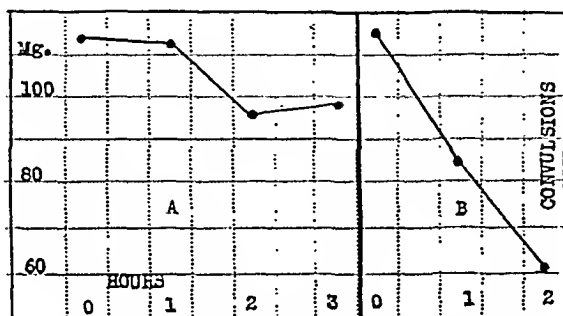


CHART 4.—Blood sugar curves obtained in a rabbit A, after the injection of gastric juice incubated with 20 units of insulin which was dissolved in alcohol and evaporated to almost dryness, and B, after the injection of 20 units of insulin.

Effect of Trypsin, Pancreatin and Bile on Insulin. The effect of intestinal enzymes on insulin, with and without alcohol, was investigated. A small amount of powdered trypsin was mixed with 20 cc. water and divided into two parts. To one part 20 units of insulin were added and incubated for about 40 minutes, and then injected. To the second part 20 units of insulin dissolved in 10 cc. of 95% alcohol were added and incubated for about 40 minutes. The insulin was extracted and injected, and the blood sugar levels were determined over a period of 3 hours. After the injection of the first part into rabbits there was very slight variation in the blood sugar level. In contrast, after the injection of the second part, there was a sharp drop in the blood sugar level. Typical illustrations of the results are shown in Chart 5. These results suggested that trypsin, like gastric juice, destroyed insulin, and this digestion was prevented when the insulin was dissolved in alcohol.

The same type of experiments were made using pancreatin instead of trypsin. Similar findings were noted and typical examples are shown in Chart 6.

The effect of bile on insulin was tested by adding 20 units of insulin to 10 cc. of bile and incubating for 1 hour. This was injected and the resultant blood sugar curves were compared with those observed when bile alone was employed. The bile was obtained at operation on patients who had gall bladder disease. In 2 cases the

bile was taken from the gall bladder and in 1 case from the gall bladder and common duct simultaneously. The results obtained were variable as shown in Chart 7. For example, in 1 case, after the injection of the insulin-bile mixture, there was a maximum de-

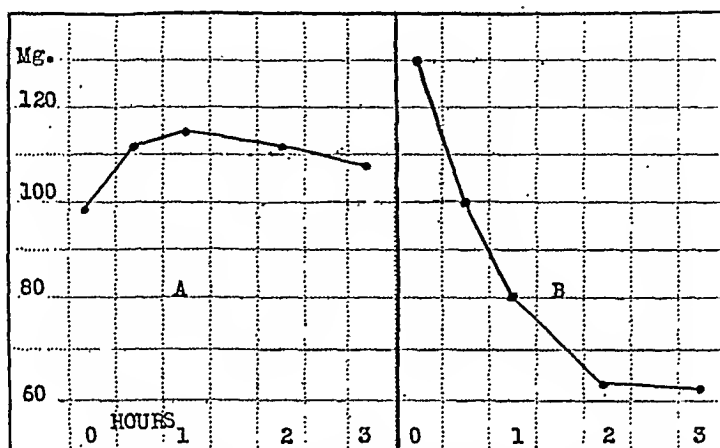


CHART 5.—Comparative blood sugar curves obtained in a rabbit A, after the injection of 20 units of insulin incubated with trypsin, and B, after the injection of an extract of 20 units of insulin dissolved in alcohol and incubated with trypsin.

crease of only 40 mg. in the blood sugar level, whereas in another case, there was a marked drop in the blood sugar level and the rabbit became convulsed within 3 hours. When bile was injected there was no significant change in the blood sugar concentration. These results suggested that bile is probably not a very significant factor

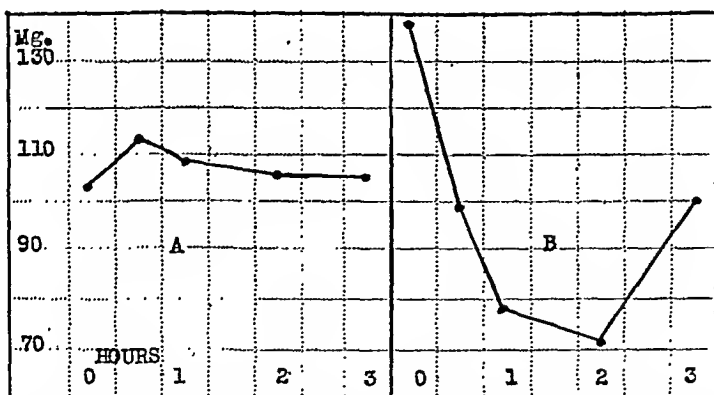


CHART 6.—Blood sugar curves obtained in a rabbit A, after the injection of 20 units of insulin incubated with pancreatin, and B, after the injection of an extract of 20 units of insulin dissolved in alcohol and incubated with pancreatin.

in the inactivation of insulin. Nevertheless, it may be to some extent an inhibitory factor in certain cases with gall bladder disease.

The Oral Administration of Insulin in Alcohol. As the result of the previous experiments, it was reasonable to conclude that insulin

dissolved in a sufficient amount of alcohol with a proper concentration was not destroyed by gastric juice, trypsin or pancreatin. An attempt was made to determine whether or not this fact can be made of clinical value in the treatment of diabetes mellitus. Seven diabetic patients and three rabbits were given orally 40 to 200 units of insulin in 30 to 60 cc. of 48% alcohol to study this phase of the problem.

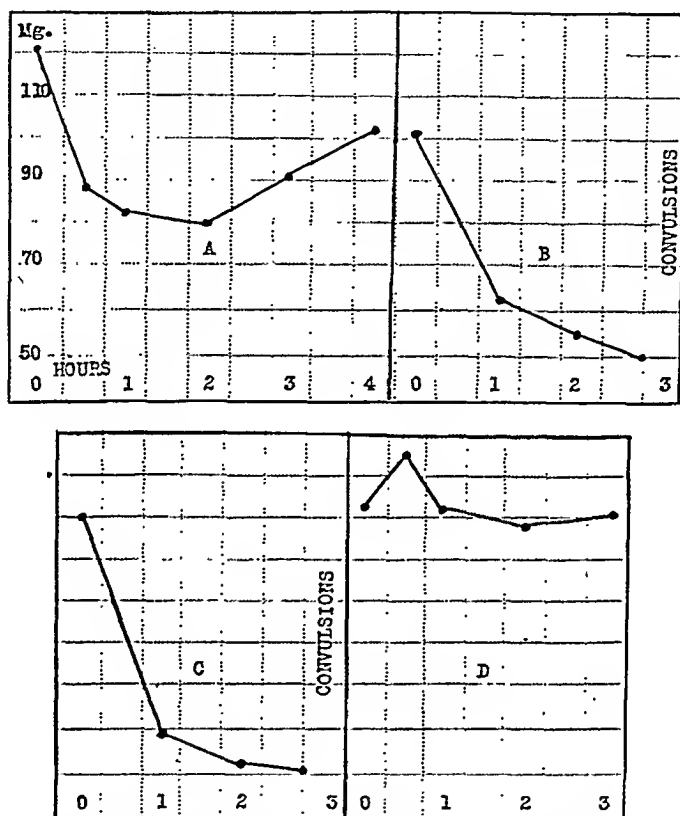


CHART 7.—Relative blood sugar curves obtained in a rabbit after the injections of A, 20 units of insulin incubated with bile from the gall bladder of a patient, B and C, 20 units of insulin incubated with bile obtained from the gall bladder and common duct respectively of another patient, and D, bile.

The blood sugar concentration was determined fasting and at hourly intervals for 6 hours after the intake of the alcoholized insulin. These blood sugar curves were compared with those obtained when alcohol alone was ingested. The results were disappointing. In the patients with diabetes after the ingestion of the alcoholized insulin there were maximum reductions of 46 to 129 mg. during the periods of observation. Nevertheless, these results were not significant because the maximum decreases observed in the

corresponding control tests were practically identical. In the rabbits there was also no important variation in blood sugar level following the intake of the alcoholized insulin. In 1 patient with diabetes 100 units of insulin in 30 cc. of 95% alcohol was introduced into the duodenum with a stomach tube and under the fluoroscope. The resultant blood sugar curve was insignificant.

The cause of these failures was investigated by administering orally 100 units of insulin dissolved in 30 cc. of 95% alcohol to 7 patients. The gastric contents were aspirated in $\frac{1}{2}$ to 1 hour, and an attempt was made to extract insulin. The extracts were injected into rabbits, and the resultant blood sugar curves were determined. From the results obtained it appeared that a large amount of insulin was recovered in 1 case, small amounts in 3 cases and no insulin in 3 cases. In the last 3 cases it was difficult to tell whether the insulin had been digested in the stomach or whether the insulin had passed out of the stomach into the intestine and could not be aspirated. However, in 4 cases at least it could be demonstrated that the insulin in alcohol was not digested entirely in the stomach in $\frac{1}{2}$ or 1 hour's time.

It appears from this work that insulin in alcohol, administered orally, has no significant effect on the blood sugar due to the lack of absorption from the gastro-intestinal tract. On the other hand, it is possible that the alcohol becomes absorbed and allows the insulin to be destroyed by the enzymes.

Summary. This paper presents a study on the effect of gastric juice, trypsin, pancreatin and bile on insulin and the protection of insulin with alcohol from digestion in 116 experiments.

The results suggest that these enzymes, except bile, digest and render insulin inactive *in vitro*. This effect does not occur when insulin is dissolved in alcohol. The protection thus afforded is probably caused by the destruction of the digestive enzymes by alcohol and not that insulin enters into any special combination with alcohol.

Insulin in alcohol administered by mouth has no significant effect on the blood sugar level. This is probably due to the lack of absorption of insulin from the gastro-intestinal tract although it is possible that the alcohol becomes absorbed and allows the insulin to be destroyed by the enzymes *in vivo*.

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THE ADVANTAGES OF VACUUM DRIED COMPLEMENT FOR USE IN THE ROUTINE WASSERMANN REACTION.

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FLOSDORF and Mudd¹ have recently described a vacuum apparatus for dehydrating serum from the frozen state. The term "lyophile" has been applied to the dehydrated product. Eagle, Strauss and Steiner² have pointed out the advantage of lyophile complement as compared with other methods of preserving complement. They ran Wassermann tests with 3477 sera and spinal fluids and obtained results using lyophile complement which were indistinguishable from complement freshly bled and salted for use within a 3 to 4-day period.

Through the coöperation of Dr. Harry Eagle we have obtained sufficient lyophile complement to permit us to use it exclusively in our routine Wassermann tests. It has been supplied in lots of from 100 to 300 cc., distributed in small vials containing from 8 to 12 cc. each. They were kept at 8 to 10° C., and were sealed before removal from the lyophile apparatus so that the dry complement was kept in vacuum. When needed for use, distilled water was added in amounts

equal to the original amount of complement. As nothing but water was removed from the complement during the dehydration process, only water was replaced. Upon the addition of the water, the dry porous material rapidly dissolved and the solution resembled fresh complement as far as could be determined. A vial from each lot was tested for hemolytic activity before it was accepted for routine use.

We have used this lyophile complement in our routine Wassermann tests for over a year and a half. During this period Wassermann tests were conducted 3 times a week. Tests were performed upon 12,175 sera and 675 spinal fluids. Fourteen lots of complement have been used and over 250 vials have been titrated and used in these tests. Not once has the lyophile complement proven unsatisfactory, or the cause of any irregularity in the tests. The advantage of having satisfactory complement ready for use at any time is obvious. The uniformity in the potency of lyophile complement can be attributed to the fact that the sera of a larger number of guinea pigs can be pooled than is ordinarily the case.

Stability of Lyophile Complement. Eagle, Strauss and Steiner have shown that lyophile complement retains its hemolytic activity for at least 8 months. This was the longest period tested. For the purpose of studying the stability, we set aside a vial or two from each lot of lyophile complement when received. These vials were tested at intervals to represent complement of various ages. One hemolysin was used in this series of tests which was designated as Hemolysin B. It was about 2 years old when the tests were started and its titer was fairly stationary. At intervals its titer was determined with fresh complement. Table 1 shows the hemolytic activity of lyophile complement of various ages, and also the result of the complement titration which was done at the same time using two units of hemolysin.

A study of Table 1 shows that all lots of lyophile complement ranging in age from 1 to 52 weeks inclusive had satisfactory hemolytic activity when compared with fresh complement. It appears from these tests that there was no loss of activity up to and including 52 weeks. The five lots which were over 52 weeks of age (55, 56, 58, 59 and 60 weeks), all showed some loss of hemolytic activity. Three of the five showed sufficient activity to give satisfactory complement titrations with two units of hemolysin. Confirming these results, obtained in actual practice, Eagle (personal communication) has found that the dehydrated complement generally begins to show demonstrable deterioration after 12 months storage in the refrigerator. It is quite possible that with technical improvements in the lyophile process, longer periods of perservation may be achieved.

Fixability of Lyophile Complement. It was thought advisable to determine whether lyophile complement of at least a year old was as readily fixed as fresh complement in the Wassermann reaction. For this purpose several positive sera were tested at the same time

TABLE 1.—HEMOLYTIC ACTIVITY OF LYOPHILE COMPLEMENT.

Age of Complement (weeks).	1	2	3	5	5	6	6	9	10	11	14	16	20	36	36	37	47	49	0	0	52	52	52	55	0	56	58	59	60	0	
Hemolysin titration (thermolysin B)	x	x	x			x			x	x	x	x	x	x	x	x		x	x	x		x			x					x	
0.5 cc.																															
0.45																															
0.40																															
0.35																															
0.30																															
0.25																															
0.20																															
Lot No. of Complement	2	3	3	1	5	7	6	1	8	12	9	10	11	14	4	5	9	4	3	F	6	F	10	14	11	F	13	8	9	11	F

a = Incomplete hemolysis in 1 to 5,000 dilution with cells 4, 7 and 11 days old.

b = Incomplete hemolysis in 1 to 1,000 dilution.

F = Fresh complement.

with lyophile complement 56 weeks old and fresh complement. The complement used was lot 13 which, as shown in Table 1 had lost some of its hemolytic activity but still gave a satisfactory complement unit when tested with two units of amboceptor. The results obtained indicate that the lyophile complement was just as readily fixed as fresh complement.

TABLE 2.—A COMPARISON OF THE FIXABILITY OF FRESH AND 56 WEEKS OLD LYOPHILE COMPLEMENT.

Amount of serum.	Serum No. 1.		Serum No. 2.		Serum No. 3.		Serum No. 4.		Serum No. 5.	
	Fresh comp.	Lyo comp.	Fresh comp.	Lyo comp.	Fresh comp.	Lyo comp.	Fresh comp.	Lyo comp.	Fresh comp.	Lyo comp.
0.2 cc.	4	4	4	4	3	3	±	±	4	4
0.1 cc.	4	4	4	4	1	±	—	—	4	4
0.05 cc.	3	3	2	2	—	—	—	—	3	2
Control	—	—	—	—	—	—	—	—	—	—

Additional evidence of the fixability of lyophile complement is shown in the results of a study of 646 sera from known syphilitics in which the Wassermann test using lyophile complement was compared with the Kahn and Eagle flocculation tests. The Wassermann test in this series proved to be as sensitive as the Kahn test. A complete report of these tests will be published elsewhere.³

Conclusions. Complement dehydrated from the frozen state and sealed *in vacuo* ("lyophile" complement), when stored in the refrigerator at 8° to 10° C. retained its full hemolytic activity and fixability for a period of 12 months. Both the complement and hemolysin titrations remained approximately constant over this entire period. Thereafter deterioration was detected. This complement has been used in 12,175 blood and 675 spinal fluid Wassermann tests and has proved in all respects equivalent to fresh complement. We have discontinued our guinea pig colony because of the greater convenience and uniformity of this type of complement.

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BOOK REVIEWS AND NOTICES.

TWENTIETH CENTURY PSYCHIATRY. Its Contribution to Man's Knowledge of Himself. By WILLIAM A. WHITE, M.D., M.A., Sc.D. Pp. 198. New York: W. W. Norton & Co., Inc., 1936. Price, \$2.00.

THIS volume is one of the series based on the Salmon Memorial Lectures. It is concerned with psychiatry as a medical specialty, the social significance of psychiatry and the general implications of psychiatric thought. Of this period was Kraepelin, whose outstanding achievements were in the dementia præcox and manic depressive psychoses. At about the same time Binet and Simon did their research in feeble-mindedness and developed their intelligence scale. Freud, elaborating upon the studies of Janet, gave us psychoanalytic psychology. America's contribution was mental hygiene, with which movement Salmon was so intimately identified, and which now lays claim to branches in all civilized countries.

In the discussion the increasing number of psychiatric patients, the movement to keep them at home as long as possible is heartily approved. For many centuries this method has been in operation in Gheel, Belgium, but the author does not mention its recent employment in Massachusetts and New York.

This thesis shows a compromise between a technical and a popular rendering, giving consideration to aphasia, crime trials with their absurd hypothetical questions, "gestalt" psychology, heredity, sterilization and diverse other subjects.

N. Y.

DENTAL INFECTION AND SYSTEMIC DISEASE. By RUSSELL L. HADEN, M.A., M.D., Chief of the Medical Division, Cleveland Clinic, etc. With a Foreword by DR. EDWARD C. ROSENOW, Pp. 163; 63 illustrations. Second edition, revised. Philadelphia: Lea & Febiger, 1936. Price, \$2.50.

AN accurate and convincing presentation of an important subject. There are discussed the bacteriology of dental infection, with a most interesting correlation of culture findings with radiographic and clinical examinations of pulpless teeth; the pathogenicity of the organisms found in dental infection; the types of diseases which may arise from dental focal infection; the experimental proof for the relation of infected teeth to such metastatic disease. The book is warmly recommended both to physicians and dentists.

R. K.

AN INDEX OF DIFFERENTIAL DIAGNOSIS OF MAIN SYMPTOMS. By various writers. Edited by HERBERT FRENCH, C.V.O., C.B.E., M.A., M.D., (OXON.), F.R.C.P., (LOND.), Consulting Physician to Guy's Hospital; late Physician to H. M. Household. Pp. 1145; 742 illustrations (196 in colors). Fifth edition. Baltimore: William Wood & Co., 1936. Price, \$16.00.

NEW diagnostic tests are devised from time to time; many of these do not survive, but a few prove themselves to be of permanent worth—the Aschheim-Zondek test for pregnancy, for example; the technique of established methods improves—pneumatography, for instance, and methods of exam-

ining the gall bladder and the Fallopian tubes have made great strides in the last few years; rare diseases such as tularemia, botulism, psittacosis, pink disease, become less unfamiliar; the result being that, although the main factors in differential diagnosis are permanent, this work has to be re-edited from time to time.

Many tests have been omitted purposely, on the ground that, as laboratory methods, their bed-rock reliability has not yet been established; but it is hoped that all those on which reliance can be placed have been included.

The original purpose of the work remains unchanged; it is intended to be a help in arriving at a correct diagnosis in cases in which one or more symptoms are pronounced and yet the real nature of the malady is not immediately clear. It would seem that the book serves a useful purpose for it has already reached its 53rd thousand. (From the Preface to the fifth edition.)

AMERICAN MARTYRS TO SCIENCE THROUGH THE ROENTGEN RAYS. With a Short Glossary of the Scientific Terms Used in the Text. By PERCY BROWN, M.D., F.A.C.P., F.A.C.R., Historian and Former President, American Roentgen Ray Society. Pp. 276; 55 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, \$3.50.

THIS record of the lives of 28 American martyrs to the infant science of Roentgenology is indeed a labor of love by one who was the "dear friend" of most of them and himself has not come unscathed through his service to the cause. "Martyrs" also in the etymological sense of witnesses to the truths of the discipline to which their lives were sacrificed, these men (and one woman) without exception continued in the path of duty, unflinchingly and heroically, even when in most cases some of the perils of continued activity were appreciated and all possible efforts to meet these perils were made. It is good to have on record an accurate contemporary account of such men's lives, of which already some of the details were fading from view; it is still better to know that the list of sacrifices to this particular risk from now on will not be greatly increased; but perhaps best of all is to have before us the stimulating example of these unassuming heroes in their careers of unswerving devotion.

E. K.

INSULIN. ITS PRODUCTION, PURIFICATION AND PHYSIOLOGICAL ACTION. By DOUGLAS W. HILL, B.Sc. (BRIS.), Ph.D. (LIV.), Lecturer in Chemistry, University College, Exeter; Special Lecturer in Organic Chemistry, University of Bristol, and FREDERICK O. HOWITT, M.Sc., Ph.D. (LOND.), F.I.C. Foreword by Professor E. C. DODDS. Pp. 219; 6 photomicrographs and 7 tables. London: Hutchinson & Co., Ltd., 1935. Price, 12/6.

THIS monograph, for its size, covers the vast amount of literature on insulin in a surprisingly complete manner. In addition to author and subject index there are 9 chapters which not only deal with insulin but treat briefly the subjects of carbohydrate metabolism, methods for the quantitative determination of glucose, and insulin substitutes. A bibliography at the end of each chapter includes a total of over 1500 references. As the literature is so great, the authors have omitted any discussion of the clinical use of insulin. The relation of the pancreas to the other glands of internal secretion has been discussed but briefly. Anyone interested in the scientific development, and physiologic action of insulin will find this book most interesting and instructive.

J. J.

CANCER COMMISSION COMMITTEE STUDIES. The California Medical Association. (The Results of a Five-year Correlated Study by 150 Members of the Medical Profession.) Pp. 123. San Francisco: J. W. Stacey, Inc., 1936. Price, 75c.

THIS booklet reproduces material published in *California and Western Medicine* by the Cancer Commission created by the California State Medical Society in 1931. It includes concise statements from 13 committees mostly dealing with tumors of various parts of the body. While the several reports necessarily vary considerably in form and merit, they can be said to give, in general, clear statements of the kinds of tumors met and their manifestations, with sound advice as to treatment. To a pathologist, the pathologic aspects seem scantily treated even in such a practical compilation; for instance, no statements were found about such an important matter as the biopsy and the evaluation of malignancy. Representing the views of over 150 practitioners, however, this work epitomizes in convenient form a valuable cross sectional modern view of cancer. E. K.

A GUIDE TO PSYCHIATRIC NURSING. By F. A. CARMICHAEL, M.D., Superintendent, Osawatomie Hospital, Osawatomie, Kansas; Lecturer in Clinical Psychiatry, University of Kansas Medical School, Kansas City, and JOHN CHAPMAN, M.A., M.D., Sometime Associate in Psychiatry, Osawatomie State Hospital, Osawatomie, Kansas. Pp. 175; 31 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$2.25.

THIS is a small book organized for a course in psychiatric nursing and is somewhat comprehensive although concise. Having been written primarily for a State Hospital it is essentially clinical and practical.

One chapter deals entirely with the symptomatology of mental disease and its relation to care and treatment from the nursing standpoint. A good résumé on the history of psychiatry is given; a chapter on psychopathology is quite comprehensive and fairly liberal in its presentation.

Chapters on etiology and a description of the psychoses follow a clinical pattern. Although the practical application of nursing principles and technique are stressed the writers are physicians rather than nurses and the emphasis lies on theory as well as practice.

As a textbook for nurses in general training it might be too profound. For nurses taking postgraduate psychiatric work it would probably be more suitable.

In the appendix one of the authors submits a modification regarding the classification of mental disease on the basis of the description of the activity of the patient rather than the emotional state. This is out of place in the book and although interesting would not be agreeably received in many psychiatry circles. L. S.

BASAL METABOLISM IN HEALTH AND DISEASE. By EUGENE F. DU BOIS, M.D., Medical Director, Russell Sage Institute of Pathology; Professor of Medicine, Cornell University Medical College, New York; Physician in Chief to the New York Hospital. Pp. 494; 99 illustrations and 67 tables. Third edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$5.00.

"THE subject of basal metabolism has during the last few years become of considerable importance to the practitioner of medicine. Most of the literature which deals with it, however, is written primarily for research workers or physiologists. The writer has, therefore, attempted to bring

basal metabolism out of the realm of pure physiology into the domain of clinical medicine. This book is written for those engaged in the practice of medicine and surgery, for medical students, for physiologists and for dietitians. While it has not seemed necessary to give the details of the many instruments used for measuring the basal metabolism, the underlying principles of technique have been fully discussed.

"The chapters dealing with surface area and normal standards have been rewritten and rearranged in the light of the contributions of the last two years and the chapters on disease have received many additional references.

"The advance in the study of basal metabolism is not unlike the settlement of a new colony in a distant land. When the first edition of this book was written in 1924 most of the pioneers, Rubner, Zuntz, von Müller, Magnus-Levy, Benedict and Lusk were still active in the field. The frontier was expanding. At the time of the second edition in 1927 there had been a great stabilization but there was still much unexplored territory and not a few outposts in dangerous or sterile regions that have since been abandoned. The third edition comes in a period of well established settlements and relatively little exploration into new country. One important field dealing with physical channels of heat loss is, however, yielding much information and it has been a pleasure to add a new chapter on this subject." (From Author's Preface.)

GENETICS. By H. S. JENNINGS, Henry Walters Professor of Zoölogy and Director of the Zoölogical Laboratory in the Johns Hopkins University. Pp. 373; 70 illustrations. New York: W. W. Norton & Co., Inc., 1935. Price, \$4.00.

THE resemblances and differences among organisms depend upon two main factors. First, upon the material received from their parents, and second, upon conditions to which this material has been subjected. It is with the first of these factors, heredity (or, more broadly, genetics) that this book deals. The author has aimed to present his subject in such a manner that any educated person may understand it. Hence this work may be read with profit not only by the physician but by the ever increasing group of laymen whose intellectual curiosity has been stimulated by the great discoveries made in the field of genetics. Among the subjects discussed are the materials of heredity and their operation, the germ cells and the chromosomes, the genes and their relation to characteristics, the rules and ratios of inheritance, the relation of characteristics to environment, the interaction of environment with heredity, hybridization, genetic variations and mutations.

Professor Jennings' lucid presentation of his subject makes the book very readable.

B. L.

POSTMORTEMS AND MORBID ANATOMY. By THEODORE SHENNAN, M.D., F.R.C.S. (EDIN.), Professor of Pathology in the University of Aberdeen. Pp. 716; 241 illustrations. Third edition. Baltimore: William Wood & Co., 1935. Price, \$9.00.

THIS book deals with the technique of postmortem examinations and with the study of the organs as they are seen at the autopsy table. Of particular value are the instructions of how to examine each organ. First, in the case of the lung, it is stated that the principal points to be investigated are: the color of the organ, the air-content, consistency, friability, presence or absence of consolidation, the nature of the fluid escaping from the cut surfaces and from the bronchi, and the nature of abnormal cavities. Under

these several headings there is a very useful discussion which should serve as a guide not only to the undergraduate but prove of considerable help to the practising physician who occasionally has an opportunity to perform an autopsy. The book is well written and has excellent illustrations. That a third edition was demanded speaks for its continued usefulness.

B. L.

INJURY AND INCAPACITY. With Special Reference to Industrial Insurance. By H. ERNEST GRIFFITHS, M.S. (LOND.), F.R.C.S., Surgeon, Albert Dock and Hertford County Hospitals; Consulting Surgeon, Wimbledon Hospital, etc. Pp. 270. Baltimore: William Wood & Co., 1935. Price, \$5.00.

THE object of this book is to place in the hands of interested individuals a compilation of the experience gained in the handling of industrial cases. Its basis has been the records of some 50,000 case reports of a large English insurance company and some 15,000 of his own cases. He attempts to form an estimate of the probable period of disability based upon the statistical analysis of these cases. The subject matter has been arranged in anatomical groupings, *e. g.*, disabilities following injuries to the head, chest, and so on. In each group he discusses the cause of the disability, the symptoms which may arise as sequela of the injury and at the end of each section there is appended a table setting forth the statistical experience of the "average period of the incapacity from work." The estimates are given for both heavy and light work and they are further subdivided according to age and in some cases according to sex. In many of the sections, suggestions as to treatment are given from the experience of the author.

At the end of the book, the author has appended a classification of the physical requirements for particular trades. He has classified all occupations into 24 types and he describes in detail the necessary physical requirements for workmen employed in a particular trade. Thus, in Type I, the physical requirements are given for heavy, laborious work and all forms of labor on the flat; Type IV gives the requirements for electricians; Type XI, for dressmakers; Type XXIII, for crossing-sweepers, and so on. In this analysis the author points out the necessary functions and shows how certain anatomic disabilities such as loss of a finger or, in some cases, ankylosis of joints may not necessarily be disabling for certain occupations.

The book has no illustrations; it is clearly and concisely written and should have a large field of usefulness for both medical men and lawyers who are interested in industrial surgery.

L. F.

THE HAIR AND SCALP. A Clinical Study (with a Chapter on Hirsuties). By AGNES SAVILLE, M.A., M.D. (GLASG.), M.R.C.P.I., Consulting Physician to Fitzroy Square Skin Hospital, etc. Pp. 288; 54 illustrations. Baltimore: William Wood & Co., 1935. Price, \$5.00.

THOSE who have mourned the gradual passing of Jackson and McMurtry's book on diseases of the scalp from our dermatologic shelves will welcome Saville's effort to bring our somewhat tattered and discreditable knowledge of hair and scalp diseases up to date. The book contains a great deal of information, as systematically arranged on the whole as a subject of such patchwork knowledge could be. It is really remarkable to find how often the search for information on an individual point is rewarded by an excellent paragraph or two containing a discriminating review of the most recent investigations. The book follows the clinical tradition of English dermatology, but gives more than the usual regard for general

opinion and the results of special investigation by students in many fields and in the best known Continental and other groups. The approach on controversial matters is temperate and broad, as witness the account of the legendary sudden whitening of the hair. There are a number of excellent case illustrations from the author's evidently very substantial experience in the treatment of disease of the hair and scalp. The chapter on hirsuties will add a point or two to almost anyone's armamentarium of information and therapeutic crutches in such situations. The constitutional background of hair and scalp disease receives remarkable and discriminating attention, while the local management, even to the effect of modern cosmetic practices and foibles is well dealt with. The chapter on the molecular structure and elastic properties of hair, written by W. P. Aspbury, Lecturer on Textile Physics in the University of Leeds, is a genuine piece of first-rate research which has direct application, as Saville points out, to such common practices as the "permanent wave." The classifications are in the main clinical and morphologic rather than etiologic, but of course, unavoidably so. It has been necessary to lump large blocks of clinical phenomena into single patchwork chapters, such as that on pustular conditions of the scalp. This method of treatment, while regrettable as an evidence of incomplete knowledge, is a convenience from the standpoint of the clinician and practitioner. The observations on hair dyes are discriminating, useful and complete. It would seem that authors contemplating publication in a foreign country could afford to make their therapeutic recommendations and prescriptions conform more closely to the pharmacopeial terminology of their publisher's market, and this book cannot wholly escape this criticism. The useful memoranda on formulæ are, however, almost uniformly usable in American practice. For a book which happily escapes the current exploitation by and misuse of colored plates, the price seems unduly high, and will perhaps limit its usefulness regrettably to the practice of specialists.

J. S.

THE RADIOLOGY OF BONES AND JOINTS. By JAMES F. BRAILSFORD, M.D. (B'ham.), M.R.C.S. (Eng.), Hunterian Professor, Royal College of Surgeons, England, 1934-1935; Radiologic Demonstrator in Living Anatomy, The University of Birmingham, etc. Pp. 571; 340 illustrations. Second Edition. Baltimore: William Wood & Co., 1935. Price, \$9.00.

THOUGH appearing but one year after the first edition, several notable changes have been made in this excellent textbook. A chapter on Dental Radiography has been added. Several sections have been rewritten as the result of recent investigations. Some of the illustrations have been replaced.

G. W.

GREAT DOCTORS OF THE NINETEENTH CENTURY. By SIR WILLIAM HALE-WHITE, K.B.E., M.D., LL.D. (Hon.), F.R.C.P., Consulting Physician to Guy's Hospital. Pp. 325. Baltimore: William Wood & Co., 1935. Price, \$5.00.

THE nineteenth was an eventful century through the contributions made to medical progress by outstanding individual British physicians and surgeons. The author has gathered together biographical sketches of 17 distinguished men whose particular contributions became of interest not only to medical men but to the general public as well. The series extends from the last years of the eighteenth century, when Jenner discovered vaccination, to the end of the first quarter of the twentieth century, when Ross confirmed his observations on the transmission of malaria by mosquitoes.

The series might be likened to a chain as the individuals became more or less intimately associated one with another, Astley Cooper, in the field of anatomy and surgery; Charles Bell, in comparative anatomy and musculo-nervous sensation; Bright in his exposition of the morbid anatomy of the kidney; Bowman, both by his discoveries in the histology and physiology of the kidney, and as ophthalmologist and physiologic histologist; Marshall Hall, with his method of reviving the asphyxiated and his investigations of the diseases of the nervous system; Addison, who achieved the distinction of discovering two diseases both named after him; Stokes, by attention to clinical investigation and clinical teaching, especially of the affections of the heart; Simpson, surgeon and anesthetist; Paget as surgical pathologist; John Simon, in Public Health; Gull, Wilkes and Hughlings Jackson in neurology; Lister, a surgeon practising antiseptics; Manson, detecting the effects of parasites in Tropical diseases; and, lastly, Ross discovering that the anopheles mosquito is the carrier of the malaria parasite.

Mingled with these names are those of hosts of others who by their labors either aided directly their chiefs, or helped to explain or elucidate what they had presented. Many were either directly connected with Guy's Hospital or were associated with Guy's men, so that it is of further interest to see the links which bound these men into such a continuous chain. The author is himself a "Guy's man," and the book can serve as an additional monument to the greatness of his predecessors in that Hospital.

The work is beautifully printed and the text most readable; its service could have been enhanced by the inclusion of contemporary portraits of their subjects.

B. C.

MEDICAL MYCOLOGY. Fungous Diseases of Men and Other Mammals. By CARROLL WILLIAM DODGE, PH.D., Mycologist, Missouri Botanical Garden; Professor, Henry Shaw School of Botany, Washington University, St. Louis. Pp. 900; 142 illustrations. St. Louis: The C. V. Mosby Company, 1935. Price, \$10.00.

In this large volume, printed on good paper with a moderate number of line-drawings, the essentially medical, *i. e.*, disease, phases are sketchy, as might be expected where the author has the viewpoint of the cryptogamic botanist. However, in this field the greater need in medicine at present is the perspective and criticism of the botanist toward medical mycology, and these are amply and valuably expressed in this book. It is a very complete catalogue, analysis and critique of all of the fungous organisms known in mammalian disease, supplemented by a full bibliography. All of these are features which are not to be found in any other work on this subject in the English language. Keys are printed with the object of facilitating determination of species. It remains to be seen whether certain rather radical modifications of classifications, although they may be well founded botanically, will simplify an already difficult situation for the medical biologist. The book is an indispensable complement, biologically speaking, to the various treatises on clinical mycology which are widely and irregularly scattered through medical literature.

F. W.

NEW BOOKS.

Collected Writings. Alfred F. Hess, 1875-1933. In 2 volumes. Pp. 1453; 127 illustrations, 124 charts and many tables. Springfield, Ill.: Charles C Thomas, 1936. Price, \$15.00.

Neurological Surgery. By LOYAL DAVIS, M.S., M.D., Ph.D., D.Sc. (HON), Professor of Surgery and Chairman of the Division of Surgery, Northwestern University Medical School, Chicago. Pp. 429; 172 illustrations and 2 plates. Philadelphia: Lea & Febiger, 1936. Price, \$6.00.

Passive Vascular Exercises (and the Conservative Management of Obliterative Arterial Diseases of the Extremities). By LOUIS G. HERRMANN, A.B., M.D., Assistant Professor of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital, etc. With a Foreword by MONT R. REID, M.D. Pp. 288; 80 illustrations and 4 colored plates. Philadelphia: J. B. Lippincott Company, 1936. Price, \$4.00.

The Baby and Growing Child. Feeding and Health Care for Physicians, Mothers and Nurses. By LOUIS FISCHER, M.D., Consulting Physician to the Willard Parker Hospital, New York City, and St. Vincent's Hospital, Montclair, N. J., etc. Pp. 260; many illustrations, some in colors. New York: Funk & Wagnalls Company, 1936. Price, \$1.50.

Strength Out of Suffering. A Translation of *Servitude et Grandeur de la Maladie*. By FRANCE PASTORELLI. Pp. 224. Boston: Houghton Mifflin Company, 1936. Price, \$1.50.

Chinese Medical Journal, Supplement No. 1, February, 1936. Pathology and Microbiology. Being Mainly Proceedings of the Chinese Society of Pathology and Microbiology held in Canton, November 5-8, 1935. Pp. 518; 70 plates of illustrations. Peiping: Chinese Medical Journal, 1936. Price, \$2.50 or 10 shillings.

"Owing to the increasing number of papers in the field of Special Pathology and Microbiology hitherto published in the *Chinese Medical Journal* which is not primarily intended for such subjects, it is thought desirable to bring the material together in one publication; hence the issue of this first number of our Supplement series. This Supplement is of the same size and format as the regular issues of *Chinese Medical Journal* and contains over 500 pages of text and 70 plates of illustrations. Price, U. S., \$2.50, or 10 shillings. The list of contents will give some idea of the value of this publication. It is hoped that all would-be contributors will read, learn and inwardly digest the article on 'Methods of Illustrating Scientific Papers,' the ignorance of which has spoilt many a promising reputation and the temper of many an editor." (Publisher's advertisement.) We heartily-endorse the last paragraph.

Your Hay Fever. By OREN C. DURHAM, Chief Botanist, Abbott Laboratories, North Chicago, Ill. With an Introduction by MORRIS FISHBEIN and a Chapter on Treatment by SAMUEL M. FEINBERG, M.D., F.A.C.P. Pp. 264; 17 illustrations and 7 tables. New York: The Bobbs-Merrill Company, 1936. Price, \$2.00.

On Percussion of the Chest. Being a Translation of Auenbrugger's Original Treatise Entitled "Inventum novum ex percussione thoracis humani, ut signo abstrusos interni pectoris morbos detegendi." [Vienna, 1761.] By JOHN FORBES, M.D. [London, 1824]. Introduction by HENRY E. SINGERIST. Pp. 31; 2 illustrations. Baltimore: The Johns Hopkins Press, 1936. Price, 75c.

The International Medical Annual. Fifth-Fourth Year, 1936. A Year Book of Treatment and Practitioner's Index. Editor: H. LETHBY TIDY, M.A., M.D. (OXON.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S., with 36 Contributors. Pp. 555; 73 illustrations and 81 plates, some in colors. Baltimore: William Wood & Co., 1936. Price, \$6.00.

Doctor of the North Country. By EARL VINTON McCOMB, M.D. With a Preface by LOGAN CLENDENING, M.D. Pp. 238. New York: Thomas Y. Crowell Company, 1936. Price, \$2.00.

A Textbook of Histology. By JOSEPH KRAFKA, JR., Ph.D., M.D., Professor of Microscopic Anatomy, University of Georgia, School of Medicine, Augusta, Ga. Pp. 246; 95 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, \$2.50.

International Clinics. Vol. II, Forty-sixth Series, 1936. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 327; illustrated. Philadelphia: J. B. Lippincott Company, 1936.

The opening article of this number on Glomal Tumors (by Geschickter) includes an excellent colored illustration (Masson's trichrome stain) and a good exposition of the pathology of the subject. Of the 14 articles, 2 others are surgical, 2 pediatric and the rest medical.

Illustrious Contributions to Public Health. A Souvenir. Prepared for the Dedication Exercises on Tuesday, November 26, 1935. By CHARLES FREDERICK BOLDUAN, M.D., Department of Health, City of New York. Pp. 33; illustrated. Privately Printed, 1936. Price, \$1.00. (Can be obtained from the New York Academy of Medicine.)

NEW EDITIONS.

Animal Micrology. Practical Exercises in Zoölogical Micro-Technique. By MICHAEL F. GUYER, Professor of Zoölogy in the University of Wisconsin. With a Chapter on Drawing by ELIZABETH A. (SMITH) BEAN, former Assistant Professor in Zoölogy in the University of Wisconsin. Pp. 331; 76 illustrations. Fourth edition, revised. Chicago: The University of Chicago Press, 1936. Price, \$2.50.

Lehrbuch der Inneren Medizin. Vols. 1 and 2. By H. ASSMANN, G. V. BERGMANN <mit F. STROEBE>, H. BOHNENKAMP, R. DOERR, H. EPPINGER, E. GRAFE, FR. HELLER, G. KATSCH, P. MORAWITZ, A. SCHITTENHELM, R. SIEBECK, R. STAEHELIN, W. STEPP, H. STRAUB. Pp. Vol. 1, 934; Vol. 2, 846; illustrations, Vol. 1, 171; Vol. 2, 153. Dritte Umgearbeitete und Ergänzte Auflage. Berlin: Julius Springer, 1936. Price, Paper, RM 48; Bound, RM 52.

Post Mortems and Morbid Anatomy. By THEODORE SHENNAN, M.D., F.R.C.S. (Edin.), Professor of Pathology in the University of Aberdeen. Pp. 716; 241 illustrations. Third edition. Baltimore: William Wood & Co., 1935. Price, \$9.00. (Review, p. 279.)

The Extra-Ocular Muscles. A Clinical Study of Normal and Abnormal Ocular Motility. By LUTHER C. PETER, A.M., M.D., Sc.D., Professor of Diseases of the Eye in the Graduate School of Medicine of the University of Pennsylvania; Ophthalmologist to the Graduate Hospital of the University of Pennsylvania and the Rush Hospital for Consumption and Allied Diseases, etc. Pp. 351; 136 illustrations and 5 colored plates. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$4.50.

The second edition of this well-known book includes an entirely new chapter on operations on the ocular muscles, as practised by the author. Much new material has been added in the treatment of squint with fusion exercises.—F. A.

Urology in Women. A Handbook of Urinary Diseases in the Female Sex. By CATHERINE E. LEWIS, M.S. (Lond.), F.R.C.S. (Eng.), Surgeon to the Royal Free Hospital; Surgeon and Urologist to the South London Hospital for Women. Pp. 100; 31 illustrations, some in colors. Second edition. Baltimore: William Wood & Co., 1936. Price, \$2.25.

Tumors of Bone (Including the Jaws and Joints). By CHARLES F. GESCHICKTER, M.D., and MURRAY M. COPELAND, M.D., Surgical Pathological Laboratory, Department of Surgery, Johns Hopkins Hospital and University, Baltimore. With Forewords by DEAN LEWIS, M.D., Professor of Surgery, Johns Hopkins Hospital and University, and the late JOSEPH COLT BLOOMGOOD, M.D., former Clinical Professor of Surgery, Johns Hopkins Hospital and University, Baltimore. Pp. 832; 525 illustrations. Revised edition. New York: The American Journal of Cancer, 1936. Price, \$6.00.

PROGRESS OF MEDICAL SCIENCE

SURGERY

UNDER THE CHARGE OF
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BRONCHIECTASIS.

THE patient suffering from advanced bronchiectasis is a pathetic sight. He is usually an individual whose illness has lasted too long to permit his care at home by his family physician, in most cases he is not considered ill enough for hospital care, and hence he is most often seen in the outpatient department or he is permitted to care for himself as best he can without professional guidance. He is characterized by his sallow, pasty complexion and frequent cough, but more noticeably by the foul odor which has been compared, for want of more adequate description, to the odor of rotten eggs or limburger cheese. Even those who have the fortitude to attempt to carry on a gainful occupation, are prevented from earning a livelihood by the repellent odor. Normal social relations are denied him and he is compelled to live a secluded life.

This picture of the late stage of bronchiectasis does not represent the greater number of cases. However, the prognosis in the milder cases is grave since the disease as a rule becomes progressively worse.^{1,2} Findley and Graham³ state that in children, except for cases with slight dilatation of the bronchi, the condition increases in severity.

Bronchiectasis is said to be next to tuberculosis the most common of all chronic lung conditions. In fact Ochsner⁴ places it above tuberculosis in regard to frequency of occurrence. Hamilton⁵ states that of all inmates of tuberculosis sanatoria 25 to 50% are not tuberculous, a figure which seems unusually high.

The actual incidence is difficult to determine, since many of the milder forms are considered to be cases of chronic bronchitis. Others are considered to be cases of tuberculosis and are treated as such. One of our recent cases had been cared for in and out of a tuberculosis sanitarium as a case of pulmonary tuberculosis for 9 years. It is possible

that this man had pulmonary tuberculosis at one time but we were able to find no evidence of an active lesion at the time of our study.

Graham, Singer and Ballou^{6,7} have pointed out the fact that many cases of bronchiectasis are considered tuberculosis but indicate that the error may also be made in diagnosing tuberculosis as bronchiectasis. Jex-Blake⁸ states that of 29,700 patients admitted to the Brompton Hospital for Consumptives 1.9% had a clinical diagnosis of bronchiectasis. He considered this figure as being too low and gave the probable figure as 5%. Since the publication of the paper by Jex-Blake the method of diagnosis has been improved by the introduction of iodized oil as a contrast medium,^{9,10} and the incidence in a similar series would probably be higher. Lemon¹¹ reported an incidence of 0.4% from 15,500 admissions of children to the Mayo Clinic and Moll¹² also reported an incidence of 0.4% from 12,225 autopsy cases from the General Infirmary at Leeds. Ochsner⁴ reported an incidence of 92% of definite bronchial dilatation in University students in whom a diagnosis of chronic bronchitis had been made. What portion of the student body this group comprised was not stated. The incidence of bronchiectasis in hospital populations or in postmortem series varies greatly.

An attempt to obtain statistical data from a large population has proven futile. In the Department of Commerce tables compiled from the United States registration area bronchiectasis is not mentioned as a cause of death. If we assume that chronic bronchitis severe enough to cause death, might be classed as bronchiectasis on the strength of Ochsner's⁴ finding of an incidence of 92% for dilated bronchi in cases of chronic bronchitis, the death rate from this cause reaches 1.5 per 100,000.¹³ These data are not too reliable, chiefly because of inadequacy of diagnosis. The figure is likely to be too low rather than too high, due to the tendency to diagnose chronic debilitating cough as tuberculosis. During the past few years many cases of bronchiectasis with mild symptoms associated with definitely dilated bronchi have been reported.^{4,14,15}

Many theories have been advanced regarding the etiology of bronchiectasis, so many in fact that one is led at once to the conclusion that the cause of the condition cannot adequately be explained at this time by any one theory. It is apparent that the causes of bronchiectasis are numerous. One of the earliest theories of the etiology of bronchiectasis deals with changes in the wall of the bronchus and loss of contractility of the muscle.^{16,17} Both of these early authors indicated their belief in the inception of bronchiectasis within the bronchus itself—a logical viewpoint which is still held by most observers. The actual process initiating the changes found in the bronchus is not always clear. There are some who maintain that disease of the bronchus is secondary to disease in the parenchyma of the lung causing fibrosis outside of the bronchus which, due to tension from without, causes dilatation of the bronchus.¹⁸

Various types of congenital abnormalities have been suggested as a cause of bronchiectasis. Chief among these abnormalities, especially in children, which have been suggested as important etiologic factors is congenital pulmonary atelectasis.^{19,20,21}

Partial obstruction of the bronchi is associated frequently with bronchiectasis. Bronchiectasis is also found associated with foreign bodies and with bronchogenic carcinoma. Occasionally bronchiectasis is thought to result from tuberculosis as a sequel to associated bronchial obstruction and atelectasis. However, Boyd¹ could find no relationship between the two diseases in the cases which she studied.

That inflammatory changes are found within the bronchial wall in cases of bronchiectasis is so well known that the question as to whether the inflammation is the cause or result of dilatation of the bronchi is an important one. In the majority of instances the infection, if not the sole inciting cause, is at least an important factor in the damage to the wall of the bronchus and the progression of the condition. Except for the cases of congenital atelectasis, antecedent respiratory infection usually precedes the onset of bronchiectasis. Bronchopneumonia, influenza and pertussis are frequently found to have been inciting causes. Table 1 illustrates the relative frequency of the occurrence of respiratory diseases as etiologic factors in bronchiectasis.

TABLE 1.—INFECTIONS LEADING TO BRONCHIECTASIS.

Author.	Total No. of cases.	Pneumonia.	Per- tussis.	Measles.	Influenza.	Bron- chitis.	Upper respiratory infection.	Other causes.
Thorpe ²²	53	23	14	9	3	..	2	2
Lemon ¹¹	63	11	27	8	15	9	16	5
Boyd ¹	60	23	10	9	4	7	..	10
Moll ¹²	65	27	6	..	1	14	..	17
Wall and Hoyle ¹⁵	20	15	11	5	4			

In favor of the premise that the bronchiectasis is the result of infection is the work of Smith²³ and Pilot and Davis²⁴ who were able to recover spirochetes and fusiform bacilli from the majority of the cases of bronchiectasis studied. These organisms are commonly found in the mouth. In addition to finding spirochetes and fusiform bacilli, Smith was able to reproduce pulmonary lesions in the rabbit by intratracheal inoculation of fusospirochetal material.

The frequent finding of spirochetes and fusiform bacilli in cases of bronchiectasis does not constitute valid evidence that the organisms are responsible for the initiation of the disease. The experimental production of lung suppuration²⁵⁻²⁸ indicates the possibility that certain cases are due primarily to the aspiration of material from the mouth into the lung and this offers one explanation for the production of lung abscess and bronchiectasis following tonsillectomy.

In a study of the bacteriology in cases of bronchiectasis Robinson and Greery,²⁹ and Boyd¹ report no predominating organisms. Ermatinger³⁰ likewise reported a wide variety of organisms from the sputum of bronchiectatic patients. Varney³¹ reported the finding of the bacillus malnogenicum of Oliver and Wherry in 94% of unoperated cases of chronic lung abscess. He also found, by cultural means, *B. fusiformis* in all cases studied. Suffice it to say that a study of the sputum has not answered the question whether the organisms found were the causative agents or secondary invaders. It has been frequently suggested that

in addition to the infectious agents it is necessary to have other factors present, such as obstruction or trauma. In any case the mixed infection which is usually present is an important factor in the disease.³² The relation of symbiosis of organisms in the production of necrotizing lesions has been well illustrated by Mason and Koch³³ to result from human bites.

The frequent occurrence of upper respiratory and sinus disease either antecedent to or associated with bronchiectasis has been referred to above. The thought that inflammation of the paranasal sinuses might contribute to the formation of ectatic bronchi has been frequently mentioned.^{14,34-38}

Graham³⁵ has noted that during attacks of sinus disease in patients with bronchial fistulae, the amount of discharge from the fistulae increases. The increase of bronchorrhea during sinus attacks suggests that the entire respiratory tract is affected. The cause for this phenomenon is not apparent. That the excess secretion in the bronchi during paranasal sinus infections might be a factor in the production of bronchiectasis due to puddling is a possibility. Kern and Schenck³⁹ point out that chronic pulmonary infections likewise cause a reinfection of the nasal sinuses and thus a vicious cycle results.

In regard to our present knowledge of the etiology of bronchiectasis, contributing factors rather than a single cause should be considered. Graham, Singer and Ballou^{6,7} state that "up to the present time it must be admitted that there is no prophylactic measure which carries with it the assurance that its employment will avoid the development of bronchiectasis." Nevertheless, careful study of each case should be made with respect to the factors involved, in the hope that these factors may be better understood and measures instituted for their correction early enough to prevent the inception of advanced bronchiectasis.

Within recent years several authors⁴⁰⁻⁴³ have discussed the pathologic findings in bronchiectasis. The material for these studies was obtained from autopsy specimens and tissue removed at operation. As might be expected, the observations corroborate the description of such material to be found in earlier papers and textbooks of pathology. Erb's⁴⁰ observations were made upon material obtained from children whose symptoms had lasted from 2 weeks to 5½ years. Realizing that the time element in the development of bronchiectatic lesions is not the only factor in the progression of the condition, he was able, however, to obtain specimens from patients in whom the duration of the disease was known and which showed varying stages of bronchiectasis. Erb was led to believe from his study that bronchiectasis is a progressive disease, and that two main stages may be recognized in the course of the disease: (1) the stage of damage or destruction and (2) the stage of repair. In those patients, the duration of whose disease was 6 weeks or less, there was no sign of regeneration of epithelium or of fibrosis. The specimens showed a purulent exudate within the bronchioles, ulceration of the mucous membrane, necrosis of a large part of the bronchial wall and the presence of exudate in the surrounding alveoli. In the early cases individual bronchi were dilated to varying degrees, the damage occurring somewhat irregularly within the bronchus. The first evidence

of repair was found by Erb⁴⁰ after 6 weeks following the onset of symptoms. This was evidenced by the appearance of epithelium approaching the squamous type instead of the normally occurring ciliated epithelium.

There appeared then a vascular granulation tissue lining the wall of the bronchus. The destroyed muscle and elastic tissue of the bronchus was wholly or in great part replaced by granulation tissue. Specimens from children whose disease was of several years' standing, showed marked fibrosis and thickening of the wall of the bronchi, with dilatation. The mucous membrane was thrown in folds and only occasionally ciliated epithelium was found. The parenchyma of the lung in the proximity of the bronchiectatic areas was fibrotic. Erb⁴⁰ believed that bronchiectasis has its origin in an acute respiratory inflammation and that obstruction favors the inflammatory process by prevention of drainage. Robinson,⁴¹ studying specimens in much later stages than those described by Erb, noted that ciliated epithelium was consistently present, and the subepithelial tissue was of a granulomatous character. In addition to loss of muscle and elastic tissue the cartilaginous plates were in some instances replaced by fibrous tissue. Of importance is the fact that in 65% of the cases Robinson⁴¹ found intimal thickening leading to stenosis of the bronchial arteries. The significance of these obliterating changes in the arteries is not known. While they are probably the result of inflammatory changes affecting all the tissues of the bronchus, it is likely that the reduced blood supply is associated with maintenance of the chronicity of the condition. This has been offered as one of the possible causes of bronchiectasis. To us, it appears more to be the result of the process than the cause.

Sehneider⁴² differentiates between atrophic and hypertrophic changes in the bronchi. In atrophic bronchiectasis he feels that the dilatations are likely to be cylindrical; in the hypertrophic, either cylindrical or saccular. In the hypertrophic form all layers of the bronchial wall are affected, while in the atrophic form, changes are found chiefly in the epithelial membrane. Since the atrophic form may change into the hypertrophic form this differentiation is not of great moment. Sehneider believes, however, that the origin of these two forms is different, the atrophic form resulting from increased intrabronchial pressure; the hypertrophic resulting from infection of the bronchi subsequent in many instances to parenchymatous lung infection. This differentiation would not appear to be significant. Of more importance is the extent of the lesion and the amount of infection present. Ballon and Ballon,⁴⁴ and Bendove and Gershwins⁴⁵ have classified bronchial dilatations as regards form. Bendove and Gershwins have attempted to relate etiology, clinical picture and treatment to the type of bronchiectasis. These authors point out the need for further studies in the correlation of symptoms, signs and morphologic aspects of bronchiectasis. How far this relationship can be carried is difficult to state at this time. In many cases combinations of the usually recognized forms occur.

Much has been said regarding associated fibrotic changes in the parenchyma of the lung as a factor in the production of bronchiectasis. It has been frequently pointed out that fibrosis of the lung is not necessarily associated with bronchiectasis. The main pathologic findings in

bronchiectasis concern changes within the bronchi, not particularly related to parenchymal changes, so that it seems fair to conclude that associated parenchymal inflammation or fibrosis is the result and not the cause of bronchiectasis.

The clinical history and signs of bronchiectasis are quite variable. In the early stages or in the mild cases the physical findings may be quite insignificant. It is in this early period that it is important to detect the presence of changes in the bronchi. The usual diagnosis which is made in these cases is that of bronchitis and the usual symptom is a persistent cough. The cough is usually paroxysmal, more likely to occur at night when the patient lies down and may not be productive. If productive, the amount of mucoid sputum expectorated is as a rule small. Occasionally the sputum may be found to be blood-streaked. Seldom is the amount of blood brought up of a measurable quantity. In the mild cases fever is slight, if present. The patient may complain of feeling just a "bit below par," tiring easily and not feeling quite as energetic as usual. The onset of these symptoms is usually associated with an upper respiratory infection. The patient may have had an acute pulmonary infection or tracheobronchitis from which he did not seem entirely to recover. No less vague than the clinical history are the physical findings. In many of the early cases, even with the most careful examination, it may be impossible to detect any abnormal physical signs. The percussion note is usually normally resonant and equal on both sides of the chest. Fremitus, vocal or tactile, is not unusual. Expansion may be somewhat limited on the affected side. Unless a careful search is made, râles are often not heard, and if present are usually localized over small areas at the base. As a rule the râles are moist and apt to persist after coughing. Breath sounds and spoken and whispered voice sounds are generally transmitted well throughout the lung fields and may give no clue to the underlying lesion.

In later or more severe types of the disease the history and physical signs may be variable but more definitely indicate the existence of chronic pulmonary suppuration. Antecedent respiratory infection may or may not be noted by the patient as the origin of his illness. However, a history of frequent severe colds is not uncommon and many patients consider themselves so susceptible to common colds that they are led to believe that their illness is due to recurrent or persistent colds. Cough is frequent and expectoration may be copious. The amount of expectoration may vary from a few cubic centimeters to over a 1000 cc. a day. The expectorated material is watery and frothy and settles upon standing into definite layers. The odor of the sputum may not be unusual but as a rule the sputum has a rancid, or even fetid odor. In advanced cases fever is usually present, and occasionally the patient may have recurrent chills. Frequently the patient is able to correlate the bouts of chills and fever with a lessened amount of expectoration, but at times these occur even when drainage is copious.

In long standing cases there is clubbing of the fingers but the fact that a patient with bronchiectasis has clubbed fingers does not designate him as a case of long continued pulmonary disease since marked clubbing of the fingers may occur within a period of a few months.

Cyanosis and dyspnea may be present and may indicate an extensive lesion or the spread of infection to parenchymal tissue. Nausea and vomiting may occur from the odor of the sputum, from swallowing it, or may be an evidence of amyloid disease.

Physical findings vary from patient to patient, as well as in the same patient from time to time. The most consistent physical finding is the presence of moist, bubbling, râles at one or both bases, before, during and after coughing. In cases with associated pneumonitis or atelectasis or in which large sacculations are present, dullness may be elicited. Limitation of costal respiratory excursions is a common finding. The physical findings may be found to change in extent and degree following postural drainage. In regard to localization the condition is more frequently found in the left lower lobe, the right lower lobe being the next most frequently involved.

Dry bronchiectasis has been described by Bezançon and associates,⁴⁶ Scott Pinchin and Morlock,⁴⁷ Moll,¹² Wall and Hoyle¹⁵ and others. It is a form in which gross infection is absent and the chief symptoms are cough and hemoptysis. Sputum may be entirely absent or expectorated in small amounts.

As has been so frequently pointed out by various authors, the only sure way to make the diagnosis of bronchiectasis is by Roentgen-ray with the aid of a contrast medium. This has been strikingly demonstrated by the fact that since Sicard and Forestier^{9,10} introduced iodized oil as a means of contrast bronchography the number of cases correctly diagnosed has increased. Many cases considered as bronchiectasis have been found to be incorrectly diagnosed, and many patients have been found to have bronchiectasis in whom the condition was not suspected. Bronchography offers a criterion not only as to the presence or absence of bronchiectasis but as to the extent and distribution as well. It has been frequently pointed out that the ordinary chest plate without the use of contrast media is not sufficient evidence either for or against the presence of bronchiectasis.

Later stages of bronchiectasis may yield a roentgenogram which shows multiple fluid levels within the bronchi. At this stage the Roentgen-ray diagnosis is but confirmatory, as the diagnosis can be made easily from the clinical picture. In 1926 Graham and Singer⁴⁸ pointed out that dense triangular shadows in the region of the cardiophrenic area were present in bronchiectasis. The presence of triangular basal shadows was noted earlier by Armand-Delille, Levy and Maric.⁴⁹ Later Rist, Jacob and Trocme,⁵⁰ Sergent and Bordet⁵¹ and Wallgren⁵² were able to show by means of lipiodol injections that the triangular basal shadows contained bronchiectatic areas. Warner and Graham⁵³ state that "triangular shadows not only invariably indicated the presence of bronchiectasis, but they occurred frequently in the cases which we have studied." These authors state that these shadows were found in about 6% of all their proven cases of bronchiectasis. These authors also by a study of cases operated on and by animal experimentation proved that the shadows were due to atelectatic bronchiectatic lower lobes and further indicated that fibrosis of parenchyma of the lung or pleural involvement was not a necessarily associated condition. It

appears that the presence of a triangular basal shadow indicates the presence of bronchiectasis, but it must be kept in mind that the absence of these shadows does not indicate the absence of bronchiectasis. Contrast bronchography is a much more dependable criterion and while not infallible is the most accurate means of study.

During the past few years much has been written concerning the surgical treatment of bronchiectasis by lobectomy. The enthusiasm with which this form of treatment has been received, associated with the gravity of the prognosis in neglected cases, has fostered an undercurrent of opinion to the effect that other forms of treatment are of little value. Lobectomy for bronchiectasis, although suggested many years ago, was practically abandoned by 1922, undoubtedly due to the high mortality. Willy Meyer⁵⁴ reported a mortality of 50% in a collected series (16 cases). Graham⁵⁵, in 1923, reported 3 cases operated on, 2 of which died. He collected 45 additional cases from the literature, the mortality from the entire series being 52%. These figures, while indicating a mortality of consequence, hardly seem sufficient to account for the abandonment of the procedure since the cases chosen for operation were necessarily in a late stage of the disease and recovery by other means was not to be expected. Graham, Singer and Ballou^{6,7} collected a series of 212 cases of bronchiectasis with an average mortality of approximately 34%. Coryllos⁵⁶ reported a series of 87 cases operated upon by 11 different surgeons with a mortality of 55.1%.

Janes⁵⁷ reported 17 cases from Shennstone's service. Of these, 3 cases died within a week following operation, while of 3 other cases which died, one survived 245 days. Of the 17 cases, 4 were reported cured, 5 improved, and 2 cases showed no improvement. Roberts and Nelson⁵⁸ reported 10 cases in which lobectomy was performed. Two of these were for carcinoma of the bronchus with bronchiectasis. Six patients were free from symptoms, and 2 patients succumbed as a result of the operation. Graham^{6,7} has reported 6 additional cases of his own subjected to lobectomy, only 1 of which died. Other cases have been subjected to lobectomy within the past few years, many of which have not been reported.

The removal of one or more lobes of the lung for bronchiectasis has been performed sufficiently successfully by a number of surgeons and with mortalities low enough to stimulate continued use of the procedure. No doubt with additional experience the mortality will be still further reduced, as well as the postoperative morbidity.

The improvement in the mortality figures of cases recently operated on as compared to those previous to 1923 is in large part due to improvement in operative technique and anesthesia. The one-stage procedure of Brunn⁵⁹ is favored by some surgeons, while others believe that a two-stage procedure has definite advantages. The impetus for renewed attempts to remove bronchiectatic lobes surgically has come mainly as a result of better localization and understanding of the process. Many of the cases operated on before the use of iodized oil as a contrast medium for outlining the diseased bronchi were not suitable for operation. With a wider use of the procedure has come a better understanding of the criteria for the selection of cases.

Cases with many lobes involved, especially those with bilateral involvement, are not so amenable to surgical therapy as are the unilobar cases. Patients with continued septic febrile reactions are best not operated upon, unless drainage can be effected sufficient to allow the acute process to subside.

It is too early to predict the end results in the majority of cases reported as cured. Some of the patients who have been thought cured of their disease will no doubt develop other dilated bronchi or early involvement in other lobes will progress. However, the improvement brought to many warrants the continued use of the procedure. To those brought from the chronic invalidism of putrid, bronchial suppuration to health and clean breath, the risk involved must seem insignificant.

In addition to excision of the diseased lobe, two other methods of surgical removal have met with some success. Cautery pneumectomy, while a more prolonged procedure, has a lower mortality and is applicable to many cases unsuitable for radical lobectomy. Graham,⁶⁰ in a series of 54 cases of chronic pulmonary suppuration, had a mortality of 11%, improvement being noted in 41 cases.

Whittemore⁶¹ has advocated the exteriorization of the affected lobe with subsequent removal by slough caused by constriction of the pedicle. This procedure with the attendant risk of secondary hemorrhage has not been widely adopted.

Drainage of bronchiectatic cavities through the chest wall has been associated with a high mortality, 62% Mumford, and Robinson,⁶² and 73.3%, Körte,⁶³ and, unless followed by cautery pneumectomy, offers little in the way of curing the lesion.

Despite the many remarkable results attained, it must not be forgotten that methods of treatment other than surgical excision of diseased lobes are available. These methods are not only efficacious in selected cases as forms of palliative therapy but are useful and usually necessary in preparing the patient for lobectomy. Chief among the non-operative methods of treatment is drainage of the dilated cavities. The simplest method of affording drainage to bronchiectatic cavities is by means of coughing and posture. Stimulation rather than suppression of cough is indicated.⁶⁴ Frequently it is possible for the bronchiectatic patient to remain free of foul-smelling sputum, and in a fair state of health by routinely placing himself in a position favorable for emptying the dilated bronchi by means of gravity. Bronchoscopy in addition to its aid in diagnosis can materially aid in removing excessive amounts of puddled material from the bronchi.^{65,66} The relation of accessory nasal sinus disease to bronchiectasis has been referred to. The importance of treating sinus infections in cases of bronchiectasis is now well known by all those interested in pulmonary suppuration.

The use of arsenicals directed against fusospirochetal infection so frequent in putrid bronchiectasis has no merit in affecting the dilatation of the bronchi. In the control of the superimposed infection it may be of some value.

Methods of treatment designed to empty bronchi by collapsing the lung have a very limited field of usefulness. When one examines the dilated bronchi in well developed cases of bronchiectasis, it is apparent

that collapse therapy can have little effect on the resistant, thickened, dilated bronchial walls. Graham,⁶⁰ however, reported a mild case in which this treatment was efficacious.

Phrenicectomy, artificial pneumothorax and thoracoplastic operations designed to obliterate dilated bronchi have been reported as successful in the treatment of bronchiectasis. The permanently improved cases are, however, few in number. In general these procedures alone have little value in the treatment of bronchiectasis. That these procedures may actually be detrimental has been suggested by some authors.⁶⁷ Graham, Singer and Ballou^{6,7} offer the suggestion that phrenicectomy may be harmful in that it decreases the efficacy of natural mechanisms for emptying the bronchi. Associated with lobectomy these procedures have found favor either preliminary to or subsequent to the removal of the diseased lobe. At best medical treatment must be considered as palliative and not curative in well developed cases. Roles and Todd⁶⁷ reported that 10 of 14 cases of dry bronchiectasis treated medically became infected within 6 years. Of 49 cases of bronchiectasis treated medically, 23 were dead within a 6-year period and 9 were totally incapacitated. These authors feel that the results are poor not only because it fails to afford permanent relief, but because spread of the condition may and does occur in a short time and prevents patients from being suitable for radical therapy. They feel that lobectomy is the treatment of choice in all cases and warn against other forms of treatment. That these authors' pessimism concerning the efficacy of medical treatment is not wholly concurred in by their colleagues is evidenced by objections raised by letters to the *British Medical Journal* following the publication of their article.^{47,68,69,70}

The indications for the various forms of treatment at the present time are not clearly defined. Bronchiectasis has always been a difficult condition to treat and the results have been generally poor. The renewed interest in this condition during the past few years will result in a better understanding of the possibilities of various forms of treatment but not until enough time has elapsed for a study of the end results over a long period. At present there is much divergence of opinion with regard to the best procedure in early mild cases. In advanced cases with hard fixed bronchi, lobectomy offers the best means of cure. Whether any true case of bronchiectasis is ever cured by medical means is doubtful. That many are carried along in relatively satisfactory health is apparent. Whether early, mild localized cases should be subjected to lobectomy at a time when the operation is most likely to be successful, is in most cases decided by the patient, most of whom are unwilling to undergo a surgical procedure of such gravity unless quite ill. Each case requires individualization. The factors by which one may decide between palliation and an attempt at radical cure are numerous. The recent impetus to the surgical approach to this condition should clarify these factors.

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OPHTHALMOLOGY

UNDER THE CHARGE OF

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NUTRITIONAL DISEASES AND THE EYE. THE RÔLE OF VITAMIN B.

In the February, 1934, number of this JOURNAL, Benedict reviewed the subject of nutritional diseases and the eye with special reference to the effects of deprivation of vitamin A. Brief mention was made of the report by Day, Langston and O'Brien on the development of cataracts in experimental animals on a diet low in vitamin G (B₂). Further studies on the ocular lesions produced by experimental deprivation of vitamin G have been carried on by O'Brien, by Langston, Day and Cosgrove,¹ and by Yudkin and his associates.² Langston, Day and Cosgrove reported the findings in a series of young albino mice which were placed on a diet entirely adequate except for the total absence of vitamin G. Seventy-nine per cent of the animals showed keratitis after an average of 43 days of the diet, 96% developed cataracts after an average of 48 days, and 57% developed general ophthalmia after an average of 50 days of the diet. These cataracts were primarily of cortical type but went on to complete, mature opacity of the lens if the animal lived long enough. Yudkin noted lenticular changes in 6 of 8 young rats kept for 10 weeks on a diet free from vitamin G. The lens changes developed completely in 7 days. He stated, however, that lens changes had not developed in older animals that had been kept for 3 months on a diet deficient in vitamin G, and

he was not sure that these experiments could be interpreted as indicating a cause of cataract in the human. He brought out the fact that the incidence of cataract in human pellagra was not especially high. O'Brien³ was able to arrest the progress of lenticular changes in experimental animals by adding vitamin G to the diet, and in one of Yudkin's² rats an early opacity of the lens absorbed after feeding with vitamin G. Cosgrove⁵ studied a series of patients with senile cataracts from the standpoint of vitamin G deficiency. He found that the majority of them ate only small amounts of food rich in vitamin G and that persons of similar age on a balanced diet did not develop cataracts to maturity during a 6-year period of observation.

In a further study of experimental cataract, Yudkin and Arnold⁴ were able to produce cortical cataract in young rats after 70 to 94 days on a diet containing 70% lactose. Nuclear cataracts developed in young rats after 11 to 14 days on a diet containing 50% galactose, after 10 to 14 days with 35% galactose, and after 14 to 20 days with 25% galactose. In older rats, cortical cataracts developed after 21 days on a diet containing 50% galactose. Yudkin suggests that these cataracts may be caused by the disturbance of calcium metabolism induced by lactose and galactose or by the direct action on the lens of increased percentages of those sugars in the aqueous. The theory of faulty calcium metabolism is supported by the known clinical association of cataract with endemic and postoperative tetany, with rickets, and with spontaneous hypoparathyroidism.

In this country, at least, the association of ocular lesions with the vitamin G deficiency of primary pellagra has not received particular attention. The occurrence of pellagra-like syndromes secondary to gastro-intestinal disturbances and chronic alcoholism has been rather generally recognized. In 1934, Levine⁶ reported a case of bilateral acute optic neuritis in "alcoholic pellagra." The neuritis cleared up with return of the vision to normal after several months on a balanced diet with added amounts of vitamin B₂. Levine stated that Quagliano had observed pellagrins with hemeralopia; that Bietti had seen optic neuritis in many cases of pellagra; that Krylov, in Russia, among 36 cases of pellagra, saw cataract formation even in children, paleness of the nerve heads, sluggish pupils, narrow vessels, scotomas for red and green in advanced cases, diplopia, hemeralopia and hallucinations, and that Kandelaki observed diplopia, cataracts and hemeralopia. These findings might be considered to indicate general nutritional deficiency rather than specific effects of vitamin G deprivation. Bristow⁷ stated that routine and special examinations of the pellagrins admitted to the South Carolina State Hospital for the Insane had failed to reveal any very characteristic ocular lesions. A number of years ago the author had the opportunity of seeing quite a few cases of pellagra of varying degrees of severity. The only striking ocular complication noted was ulceration of the cornea in some of the more advanced cases. The eyes showed, as a rule, little inflammatory reaction, the ulcers responded very poorly to treatment and progressed to complete sloughing of the cornea in several instances.

The occurrence of ocular lesions in association with deficiencies of vitamin B₁ seems to be more definitely established than in the case

of vitamin B₂. It is true that primary beriberi is probably rare in this country. In other countries, retrobulbar optic neuritis has been reported in beriberi by Fernando,⁸ by Shimazono, and by Katajama.⁹ Katajama was able to demonstrate degeneration in the medullary sheaths and axis-cylinders of the optic nerves in experimental deprivation of vitamin B₁. Moore¹⁰ reported a high percentage of visual defects apparently on the basis of retrobulbar neuritis occurring in a group of native South African students who lived largely on a diet of cooked manioc or cassava which contains a high percentage of starch. He noted that in the early phases of the disease, vision could be restored to normal by proper additions to the diet. In the more advanced stages, the visual defects were permanent. Moore was uncertain whether the optic nerve lesion was due to a vitamin deficiency or to a direct toxic effect of the manioc. He considered the vitamin deficiency the more likely cause. In this connection the case reported by Kepler¹¹ is of considerable interest. He found bilateral optic neuritis with secondary optic atrophy associated with a beriberi-like syndrome in a colored woman who had lived for some time on a diet consisting mainly of raw laundry starch.

In this country, however, more importance attaches to the types of deficiency neuritis which occur in association with dietary deficiencies resulting from gastro-intestinal disturbances of varying sorts. Christopher, Paskind and Snorf¹² reported 2 cases in which multiple neuritis developed after operations on the biliary tract. They expressed the opinion that the neuritis was due to avitaminosis resulting from prolonged postoperative vomiting which had lasted for 41 days in the first case and 43 days in the second case. Wechsler¹³ reported 8 cases of multiple neuritis which he thought were caused by avitaminosis resulting from prolonged vomiting, gastro-intestinal disturbance, or restriction in diet. Recently, Wagener and Weir reported 2 cases of rapid loss of vision associated with nystagmus, ocular muscle paralysis, and mental confusion which occurred as complications of prolonged postoperative vomiting. The loss of vision was due in the first case to optic neuritis and in the second case to retrobulbar neuritis. The symptoms in both patients improved rapidly after the cessation of the vomiting and the addition of intramuscular doses of liver extract to a balanced diet.

Jolliffe, Colbert and Joffe¹⁴ have confirmed the belief of Strauss that the peripheral polyneuritis of the alcohol addict is attributable to the deficiency of vitamin B₁ and not to the toxic effect of alcohol. It seems probable from the observations of Shastid,¹⁵ Keefer¹⁶ and others that the deficiency of vitamin B₁ resulting from restricted diet may be at least partially responsible for the retrobulbar optic neuritis or toxic amblyopia usually ascribed to the overuse of alcohol and tobacco. Addition of vitamin A (Yudkin²) or vitamin B₁ (Shastid¹⁵) to the diet is said to hasten recovery in these cases as well as in cases of optic neuritis of indeterminate origin. It has been suggested also by Keefer¹⁶ that the retrobulbar optic neuritis seen at times in nursing mothers and spoken of hitherto as "lactation optic neuritis" may really be due to avitaminosis.

Winans and Perry¹⁷ expressed the opinion that the polyncuritis associated with pernicious vomiting of pregnancy is a deficiency disease. They found that the disease responded favorably to the intramuscular administration of liver extract and they considered the deficiency to be largely one of vitamin B₁. Optic neuritis occurs at times in pernicious vomiting of pregnancy, often in association with polyncuritis or neuronitis as reported by Berkwitz and Lufkin.¹⁸ In these cases the optic neuritis is most probably also due to deprivation of vitamin B₁. It seems probable that the hemorrhages in the retina which are seen in some severe cases of pernicious vomiting of pregnancy as reported by Stander¹⁹ are also manifestations of vitamin deficiency, whether of vitamin B₁ or vitamin C it is difficult to say. However, in a case recently reported by Wagener and Weir, the hemorrhages disappeared rapidly under intramuscular administration of liver extract.

While clinical reports of ocular lesions dependent on or associated with deficiencies of vitamin B₁ and B₂ are rather scattered as yet, in this country at least, it would seem that enough experimental and clinical data are accumulating to indicate that deficiencies of these vitamins may play a more important rôle than is generally appreciated in the causation of acute and chronic affections of the optic nerve and perhaps of the ocular muscles and of hemorrhagic lesions of the retina. The words of Winans and Perry¹⁷ might well be applied to optic neuritis and retrobulbar optic neuritis: "The nutritional background of a considerable portion of the population is such as to provide for the development of deficiency polyncuritis under a variety of conditions. Marked changes in the diet may decrease the intake of the vitamin B complex below the necessary minimum. Alcoholism, intestinal operations, and prolonged gastro-intestinal upsets, including the vomiting of pregnancy, may all serve to develop this disease. In any continued illness associated with loss of appetite, the possibility of the development of polyncuritis must be borne in mind."

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ERRATUM.

In the page advertisement in the July issue of THE NATIONAL DRUG COMPANY of Philadelphia the word grand appeared instead of the word GIANT. The paragraph should have read: "We offer a special Rag Weed Antigen Outfit complete for diagnosis and treatment of Fall Hay Fever for \$10. Contains two diagnostic tests for mixed grasses and giant and dwarf rag weeds; 1 ampul-vial each Series 'AA', 'A' and 'B' Rag Weed Antigen; 25 cc. ampul-vial Sterile Salt Solution for dilution of antigen if needed; 25 cc. ampul-vial Epinephrin 1-1000 to control local or systemic reactions."

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ORIGINAL ARTICLES.

CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL
NOCTURNAL HEMOGLOBINURIA.

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I.

THE passage of blood-stained urine engaged the attention of the earliest medical observers. Both Hippocrates¹ and Galen² attributed an evil prognosis to the occurrence of black urine. The term included not only hematuria but probably, hemoglobinuria as the modern title "black water fever" suggests. However, it was not until 1883 that Ponfick³ differentiated hematuria from hemoglobinuria and determined that the latter resulted from an antecedent hemolysis and hence, from hemoglobinemia. While all hemoglobinurias dependent on intravital hemolysis have many clinical features in common, the causes have been classified for purposes of discussion as exogenous and endogenous.

The hemoglobinurias of exogenous origin are associated with infections and intoxications and are discussed in the monographs devoted to the subject. Recently, a new member was added to this group when the discovery was made that the consumption of fish or eels containing resinous acids was followed by a malady, a feature of which is "hemoglobinuria."

The disorder is indigenous to the environs of Königsberg in Germany and is known as Haffkrankheit.⁴

Poisonous resinous acids are a byproduct of the cellulose factories of Königsberg and find their way through drainage into a nearby inlet or "Haff." All the fish and certain eels in the inlet ingest the poisonous acids and become "Haff sick." If these fish containing the resinous acids are eaten by the villagers living adjacent to the water or by their cats, cats and human beings are taken ill with this singular malady.

In man the Haff disease manifests itself by the appearance of "hemoglobinuria" and by a disorder of the musculature characterized by severe pain, stiffness and limitation of movement. The attacks have a remarkable tendency to appear paroxysmally. If the disorder leads to death necropsy discloses degeneration of the striped muscles.

The manifestations of the disease have been produced experimentally by feeding resinous compounds to fish. Cats fed on these fish also become ill and develop "hemoglobinuria" and progressive impairment of gait. At autopsy the striped muscles are grayish-red and resemble fish flesh.

We shall see later how greatly this curious Haff disease resembles a rare variety of so-called paroxysmal hemoglobinuria appearing spontaneously in man.

While referring to hemoglobinurias of exogenous origin another pertinent syndrome little known in this country should be mentioned. It is favism. In 1933, we became indebted to Thomas McCrae and J. C. Ullery⁵ for the only report of a case in the English language. Favism is caused by inhalation from blossoming bean plants of the species *vicia fave* or by ingestion of the beans, either raw or cooked. It occurs most frequently in Sicily and southern Italy. The most spectacular feature of favism is the sudden occurrence of hemoglobinuria. The symptom complex includes, however, prostration, fever and acutely developing anemia and jaundice.

Since in animal experimentation with the offending bean an anaphylactic reaction has been obtained after the animals had been previously sensitized, it has been suggested that the symptoms in man represent a hypersensitiveness to the protein of the bean and its blossom.

While the hemoglobinuria of favism is exogenous in origin, so far as the introduction of the blossom or bean into the body is concerned, there is likewise an endogenous mechanism in operation productive of the anaphylaxis which is assumed to be responsible for the disorder. Therefore, this variety of hemoglobinuria may be viewed as a transition from the exogenous to the endogenous group of hemoglobinurias which we shall now proceed to review.

II.

An endogenous causal factor is evidently the important element in the mechanism provocative of certain hemoglobinurias classified in the foreign literature as the paroxysmal hemoglobinurias.

In this country paroxysmal hemoglobinuria has been used synonymously with hemoglobinuria provoked by chilling. However, the term as used in the comprehensive German reviews includes 3

types, namely, cold, march and the so-called paralytic hemoglobinurias. A new fourth type was added when, in 1931, Micheli⁶ described a well defined clinical entity a prominent feature of which was paroxysmal hemoglobinuria. The description concerned a patient whom he as well as Mareh⁷ had seen from time to time. It is this form which the title of the present communication describes. During paroxysms, perhaps all 4 but at least 3 of these types have in common, hemolysis leading to hemoglobinemia and hemoglobinuria. Nevertheless, the exciting cause of the attack, when demonstrable, varies in these several types of paroxysmal hemoglobinurias and together with their clinical manifestations justifies their separation.

In respect to causative factors cold hemoglobinuria is best understood. Mackenzie⁹ traces the historic development of our knowledge of the 3 criteria by which this form of paroxysmal hemoglobinuria is usually differentiated: syphilis, chilling and the presence of the Donath-Landsteiner test.

The march variety as its name suggests follows excessive bodily exertion, particularly that involved in walking or marching. Fleischer¹⁰ described it first, in 1881, in the case of a soldier who after a long march suddenly voided a typically hemoglobinuric urine. The only report of a well studied case in English is that of Watson and Fischer¹¹ of London, Canada. These authors suggest that march hemoglobinuria "is an exaggeration, exemplified in certain predisposed individuals, of a more or less naturally occurring phenomenon." As corroborative evidence they call attention to the observations of Feigl¹² who found blood pigment in the serum and urine of more than half of 27 men after an army pack march of 35 kilometers. The lordotic position has been considered a decisive factor with the implication that there exists some relation between march hemoglobinuria and orthostatic albuminuria.

Not to be disregarded is the suggestion of Watson and Fischer that there is an affinity between march hemoglobinuria and the so-called paralytic hemoglobinuria that has been observed in both man and beast. The modifying epithet "so-called" is used advisedly because the discoloration of the urine in these cases has been demonstrated to be due to myoglobin, a constituent of muscle fibers, rather than to hemoglobin. Paroxysmal paralytic myoglobinuria plays a more important rôle in equine than in human pathology. The similarity of some of the clinical features and especially the resemblance of the degenerative changes in the muscles of the horse and of the few human victims of the disease warrant a short digression into veterinary medicine.

The recognition of equine "hemoglobinuria" now generally classified as myoglobinuria, antedates by many years the discovery of an analogue in human clinical pathology. The pioneer work in this line is Bollinger's contribution in 1877.¹³

Still known as "hemoglobinuria" among many veterinarians the disorder affects previously healthy, vigorous horses who have stood resting in their stalls for one or more days, but who are still feeding on their usual diet. After such a "holiday," they are taken out to work one morning when within a few minutes, the susceptible horse exhibits stiffness and lameness in one or both hind legs; urged on, the legs lose power rapidly and the animal finally sinks to the ground. Coincidentally there may be muscular twitching, sweating, dyspnea and fever. The most striking accompaniment is the dark red, "hemoglobinuric" urine. Death may ensue in the course of a few days. If a fatal issue does not take place, a residual paralytic condition with atrophy may remain for weeks, months or years. Nevertheless, complete regeneration may eventually take place. The animal that has recovered may suffer from repeated attacks; the affection is truly a paroxysmal, paralytic "hemoglobinuria." At autopsies, the muscles involved are very pale, edematous and of a grayish-yellow color like "fish flesh."¹⁴

Directing attention to the parallelism of equine paralytic hemoglobinuria with the condition he was recounting, Meyer-Betz,¹⁵ in 1910, described the case of a boy who exhibited a peculiar type of "hemoglobinuria" associated with widespread muscular paralyses.

The boy, aged 13, was admitted to Friedrich Müller's Clinic in November, 1909, in a state of collapse. Two days after an attack of abdominal pain he voided urine which was black in color. Annually, since his tenth year he had had one or two such paroxysms accompanied by great muscular weakness. In 1907, it was noted that in addition to the discolored urine the shoulder girdle muscles were atrophic, the gastrocnemius muscles were large and hard. The diagnosis was recorded as "progressive muscular dystrophy of the hypertrophic type." In 1909, following another attack of "black urine," the muscular disability while marked was "rather better than worse." The diagnosis was revised to read "muscular dystrophy." Later in the year he suffered an attack of muscular weakness "of such a degree that he appeared moribund." The urine was bloody. From such a serious state his improvement was rapid and spectacular. This time the diagnosis was hemorrhagic nephritis and muscular dystrophy. Finally, Meyer-Betz correctly evaluated the "hemoglobinuria" and differentiated the muscular paralyses and contractures from those of the classic dystrophies. The boy recovered in a few months with only a residual contracture of the right Achilles tendon.

Since Meyer-Betz' publication only 3 similar cases have been reported: Günther's¹⁶ (1924), Paul's¹⁷ (1924) and Hittmair's¹⁸ (1925). Autopsies in both Günther's and Paul's cases yielded pathologic evidence to complete the resemblance between the equine and human types of paralytic "hemoglobinuria:" the affected muscles resembled "fish flesh!" It will be recalled that the same descriptive term was used to characterize the appearance of the muscles of cats and men dead of Haff disease. In all these paralytic disorders accompanied by abnormally colored urine the pigment is apparently derived entirely or in greater part from the muscles. This origin is suggested by the pallor of the muscles to which repeated reference has been made. Secondly, anemia of any noteworthy degree such as would result from hemolysis is absent. Most important testimony of all has been afforded by the spectroscopic

disclosure of myoglobin in the blood and urine in the equine disorder¹⁹ and in the Haff disease of man.²⁰

Although the term "hemoglobinuria" persists in the literature of these paralytic maladies under consideration, all recent writers consider it a misnomer for which myoglobinuria should be substituted. It would be interesting to apply this precise spectroscopic technique to the investigation of future cases of typical or atypical paroxysmal hemoglobinuria especially of the march variety to determine if perchance, myoglobin may share in the discoloration of the urine.

III.

Reverting to the statement that the discussion in the monographs devoted to the paroxysmal hemoglobinurias in man was limited to the cold, march and paralytic varieties it will be recalled that, in 1931, Micheli added what a German author⁸ subsequently called "the fourth form." This form Micheli established from a study of 13 cases described here and there in many languages, including one in English.²⁶ Three more references to the newly recognized syndrome were given by Rosenthal⁸ in his paper published in 1932. He added a 17th case of his own and stimulated a pupil, Rudolf Meyer,²¹ to write an inaugural dissertation on the subject in 1933. An 18th case is included in the dissertation. Two further examples of the "new form of paroxysmal hemoglobinuria" have since been published and we shall now proceed to summarize an account of the course of this disorder in each of 2 patients who have been under our observation.

CASE 1.—The patient, now a married woman, is at the present time (1936) 28 years of age. She has been under observation intermittently for a little over 10 years for a disorder which first manifested itself by the passage of darkly colored urine at the age of 18.

Her mother and brother were subject to hay fever.

The patient's medical history had been previously uneventful.

In mid December, 1925, she observed after an attack of abdominal pain the discoloration of the urine just mentioned. The following night she made a similar observation. When examined several days later pallor of the skin and mucous membranes was noted; a systolic murmur, maximum over the pulmonic area, was heard; the abdominal examination was negative. The urine was dark amber, contained a trace of albumin and an occasional pus cell.

The patient was not seen again until September, 1926, when she complained of fatigability. There was a history of repeated transient darkening of the urine. A distinct anemia had developed. The red blood cells numbered 3,400,000; hemoglobin 49%; leukocytes, 4950 with a normal differential count. During the latter part of the year there were a number of paroxysms of what was now recognized as hemoglobinuria. The attacks lasted a few days during which the urine was at times almost black by reflected light and a deep Burgundy red by transmitted light. Two of the paroxysms of this period were preceded by upper respiratory infections. Icterus was now evident.

Throughout most of the year 1927 the young woman led a fairly active life. She reported that often 2 or 3 days before a menstrual period mahogany colored urine was voided. The relation to the menstrual cycle was not invariable. It was observed, however, that the most deeply pigmented urine was always voided during the night and early morning hours.

After a severe attack of hemoglobinuria prolonged to 2 weeks she entered this hospital (Unit No. 9216) on November 16, 1927. She had lost no weight, the skin and mucous membranes were pale. The sclera were tinged a light yellow. Inspection of the rhinopharynx revealed nothing abnormal. The cervical lymphatic glands were not enlarged. The lungs were clear. The systolic murmur previously noted was present. Blood pressure 128/48 mm. Neither the edge of the liver nor the spleen was palpable. The basal metabolic rate was +16. The blood smear revealed marked anisocytosis and poikilocytosis; no nucleated red blood cells were seen. Reticulocytes were 10%. The fragility of the red blood cells was normal. The Wassermann reaction was negative. The Donath-Landsteiner test was likewise negative. The blood non-protein nitrogen was 36 mg. %; sugar, 92 mg. %, cholesterol, 175 mg. %. The patient's blood was of Group II (Moss). Roentgenologic examination discovered a non-union of the base of the sacrum.

During the 3 weeks following admission to the hospital there were 2 paroxysms of hemoglobinuria of several days' duration. In some specimens of the urine red blood cells were discovered; hemoglobin and methemoglobin were demonstrated. During these attacks of hemoglobinuria auto- and isohemolysins were found in the blood only to disappear when the paroxysms had terminated.

In 1928, there was little subjective evidence of illness but the anemia persisted in varying degree, the icteric hue fluctuated, paroxysms of hemoglobinuria were frequent—all in spite of many vain efforts to prevent the attacks. The patient's activities were limited; exposure to chilling was avoided; she was given iron, arsenic, liver and potassium iodid. In the summer of 1928 an attack of hemoglobinuria lasted almost 2 months.

In January, 1929, phlebitis supervened. The left saphenous vein was affected. During the year the hemoglobin never rose above 60%; in the acute seizures it fell as low as 30%. There were infrequent attacks of pain in the right lateral abdominal region, sometimes accompanied by vomiting.

For two months of the winter of 1930 the patient was the victim of a psychosis characterized by delusions of persecution and sex obsessions. From the mental disturbance she made a complete recovery.

Having become so familiar with the characteristic features of her disorder she rarely sought medical advice during the next 4 years. In 1933, she married and cared for her own household.

For a particularly severe paroxysm of hemoglobinuria in June, 1934, she was once more admitted to the hospital. This attack was accompanied by precordial distress, the temperature rose to 102°; the pulse, 120. The red blood cells numbered 1,280,000; hemoglobin, 39%; leukocytes, 2500. The mean corpuscular volume was 90 cu. microns. There was definite jaundice. The icterus index was 16. Although the exacerbation was severe, it lasted only 3 days.

In September, 1935, the condition was complicated by the appearance of cystopyelitis. For about 4 months she had recurring attacks of fever with a maximum of 105°. The pyrexia was attributed to the urinary tract infection with the colon bacillus. In spite of the repeated febrile seizures there was only one severe paroxysm of hemoglobinuria occurring in October and lasting less than 24 hours. The hemoglobin fell to 25%. Since this attack hemoglobinuria has not returned but oxyhemoglobinemia and urobilinuria have been demonstrated repeatedly. In this period, too, comprehensive skin sensitization tests were undertaken without significant

results. The urine has contained albumin, pus cells, a few red blood cells and granular casts. The casts and amorphous detritus were stained yellow: the pigment gave the Prussian blue reaction for iron. The stool exhibited an excess of urobilin.

At present (February, 1936) while pyuria persists, there is no fever and the hemoglobin registers 60%. The subject of this extraordinary medical history has resumed her household duties and is leading a fairly normal life.

CASE 2.—An automobile mechanic, white, aged 29, was admitted to this hospital (Unit No: 48198) on March 9, 1933, complaining of attacks of discoloration of the urine and weakness of one year's duration. The patient's general health had been good.

A dark discoloration of the urine was first noted a year before admission. Subsequently there were frequent nose bleeds and hemorrhages from the gums. The patient became weak and tired readily. Dyspnea and tachycardia on exertion were prominent. There were occasional vague pains beneath the sternum. Four months before entry the symptoms were aggravated, at which time the patient observed that his urine was dark brown in the morning.

On admission his temperature, pulse and respiration were normal. Blood pressure was 120/65 mm. The skin had a yellowish tint; there was pallor of the mucous membranes. His heart was normal except for the presence of a systolic murmur. Neither the liver nor spleen was felt.

The erythrocyte count was 2,790,000; hemoglobin 62%, leukocyte count 4050; neutrophils 63%, lymphocytes 33%, monocytes 4%, an occasional normoblast was found. The mean corpuscular volume of the red blood cells was 104 eu. microns. Platelets, reticulocytes, bleeding time, clotting time and clot retraction were normal. The blood was Group IV (Moss). The Wassermann reaction was negative. In the urine albumin was present from time to time, frequently in considerable amounts. Urobilin was found almost constantly. The benzidin test was often positive. Microscopically, there were observed a few white blood cells and a rare hyalin cast as well as small brownish granules in profusion, both intra- and extracellular, the exact nature of which was not determined. Non-protein nitrogen was 28 mg. %; Van den Bergh test, 1 mg. %. The gastric juice revealed free hydrochloric acid after the injection of histamin. Roentgenologic examination showed non-union of the top of the sacrum.

During the patient's stay of 4 months in the hospital there occurred 3 spontaneous attacks of hemoglobinuria. Spectroscopic examination confirmed the presence of hemoglobin in the urine. It was noted repeatedly that the specimen voided between midnight and 6 A.M. was much darker and gave a more positive benzidin reaction than the day specimens. That this was not a phenomenon of simple concentration was proved by forcing liquids during the night so that the nocturnal output equalled or exceeded the diurnal. Under these circumstances the greatest excretion of pigment still occurred at night. After the attacks of hemoglobinuria the patient became jaundiced with an icterus index as high as 20. The Donath-Landsteiner test was repeatedly negative. During the exacerbation of hemoglobinuria early in May the liver became palpable. Further studies of the blood determined that the fragility was normal. Just after the onset of the first attack of hemoglobinuria reticulocytes rose to 10.4%.

Therapy directed toward the anemia produced only transitory improvement. Several bouts of hemoglobinuria occurred during the next few months. Thus, he continued until January, 1935, when he entered the Memorial Hospital in Richmond. Allergic studies made at this time were negative.

In March, 1935, he was transferred to the Hospital of the University

of Pennsylvania.* Red blood cells were 1,900,000; hemoglobin, 31%; leukocytes, 9000 with a normal differential count; reticulocytes, 37%. Hemolysis began at 0.50% salt solution and was complete at 0.35%. With the hope of favorably influencing the hemolytic process splenectomy was performed on April 15, 1935. Before operation two transfusions were followed by severe reactions with fever and hemoglobinuria; while post-operative transfusions proceeded uneventfully without any unpleasant sequelæ. The spleen weighed 360 gm.; the sinuses contained a moderate amount of blood, the splenic pulp was normal.

A few days after splenectomy the patient developed otitis media and mastoiditis for which mastoidectomy was performed. A streptococcus septicæmia supervened. From these he recovered, so that in September, 1935, he was discharged improved but continued to have paroxysms of hemoglobinuria and was still markedly anemic.

The patient's present condition (December, 1935) is aptly expressed in his own words: "On my best days, the urine is black only in the morning; on the worst, it is black throughout the entire 24-hour period."

With the addition of these 2 cases, 22 examples of a peculiar disorder accompanied by paroxysmal hemoglobinuria are now recorded† (Table 1). From the first case published by Chauffard and Troisier,²² in 1908, to the present day the disorder under consideration has received many titles. Marchiafava⁷ called it "*anemia emolitica con emosiderinuria perpetua*;" Hijmans van den Bergh²³ had named it "*ictère hémolytique avec crises hémoglobinuriques*;" Enneking,³¹ "*hemoglobinuria paroxysmalis nocturna*" while Rosenthal commemorating the basic work of Marchiafava and one of his collaborators, suggested the Italian's title, adding "of the Marchiafava-Micheli type." We venture to describe the symptom complex as chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria. The title implies the prolonged duration of the disorder, the fundamental hemolytic state and the characteristic attacks of hemoglobinuria. It does not include the term icterus which is a concomitant of the hemolysis, because its inclusion may perpetuate the confusion with well known forms of hemolytic jaundice from which it should be separated. In the interest of brevity we shall hereafter often refer to the condition as chronic hemolytic anemia.

Chronic hemolytic anemia chiefly affects males. Of the 22 patients under consideration only 6 are women. The age incidence of onset lies chiefly in the third and fourth decades; the youngest is Scheel's²⁷ patient of 15, while the oldest is Salén's²⁹ who was 47 years of age.

In none is there a family history of the disease or of any allied disorder. Previous illnesses apparently play no predisposing part: neither syphilis nor malaria is a causal factor. The onset is insidious; increasing pallor and varying degrees of jaundice are usually the first signs of ill health. Pain in the abdomen and back may be the initial symptom.

* The patient was admitted on the service of Dr. O. H. P. Pepper, to whom we are indebted for the privilege of quoting from his records.

† Since this paper was written two additional references to case reports of this malady have come to our attention: Falkiewicz, A., and Musial, W., *Klin. Wehnschr.*, 14, 1078, 1935, and Trestini, S., *Polielinico (Sez. med.)* 42, 550, 1935.

TABLE 1.—SUMMARY OF DATA CONCERNING REPORTED CASES OF CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA.

Case.	Authors.	Date of report.	Sex.	Age at onset.	Symptom of onset.	Duration of disease at time of report (years).	Operations.	Outcome at time of report.
1	Chauffard and Troisier ²¹	1908	M.	"Young"	Abdominal pain and jaundice	6	Cholecystostomy	Living.
2	Hijmans van den Bergh ²³	1911	M.	35	Jaundice	12		Living.
3	Marchisfava and Nazario ¹⁴	1911	M.	23	Abdominal pain and jaundice	8	Cholecystotomy	Died of "grippe."
4	Biffes ²⁵	1915	M.	25	Weakness and jaundice	3	Splenectomy	Died after operation.
5	Giffin ²⁴	1923	F.	28	Jaundice	3	Living.
6	Scheel ¹⁷	1925	F.	15	Anemia and jaundice	2	Living.
7	Maninis ¹⁸	1927	M.	43	Jaundice	1	Living.
8	Salén ²²	1927	M.	47	Weakness, jaundice and hemoglobinuria	4	Nephrotomy	Died of pneumonia.
9	Villa ³⁰	1928	F.	17	Abdominal pain and enlarged spleen	5	Living.
10	Ennelings ²¹	1928	M.	37	Lumbar pain	1	Died of mesenteric thrombosis.
11	Saxl ¹²	1928	M.	36	Hemoglobinuria	"Years" 1 8	Splenectomy	Living.
12	Barta and Görög ²³	1929	M.	34	Lumbar pain and anemia		Splenectomy	Died after operation.
13	Donati ²⁴	1930	M.	28	Chills, fever and hemoglobinuria		Splenectomy	Living.
14	Marchisfava ¹⁷ and Micheli ⁹	1931	M.	22	Anemia	9	Splenectomy	Died.
15	Ilitzenberg ²³	1931	F.	32	Anemia and jaundice	3	Living.
16	Nazari ²⁶	1931	M.	19	Weakness and anemia	1	Living.
17	Bergmark ²⁷	1931-	M.	34	Abdominal pain, anemia and jaundice	6	Appendectomy; cholecystectomy	Died after operation.
18	Rosenthal ¹⁹	1932	M.	19	Chills, fever and hemoglobinuria	33	Splenectomy	Died after operation.
19	Iglauer and St. Frenreisz ²³	1934	M.	38	Jaundice and hemoglobinuria	4	Living.
20	Sehally ²²	1935	F.	25	Anemia	4	Splenectomy	Living.
21	Hamburger and Bernstein	1936	F.	18	Hemoglobinuria	10	Living.
22	Hamburger and Bernstein	1936	M.	28	Hemoglobinuria	4	Splenectomy	Living.

Soon or late there are added to the anemia and icterus, paroxysms of hemoglobinuria. In our 2 patients the discoloration of the urine led them to seek medical advice. On the other hand, years may pass before the inception of evident hemoglobinuria.

Once the syndrome is established the symptoms and signs are subject to remissions and exacerbations. The therapeutic measures now at our command do not prevent the patient from remaining anemic and icteroid though able to carry on his activities in a modified way. However, without obvious cause he will suffer from sudden attacks during which the anemia increases, the conjunctivæ and skin will assume a deeper yellow color. Chills and fever may be accompaniments. He may be annoyed by precordial distress or by abdominal and lumbar pain. The patient is prostrated and temporarily disabled. When hemoglobinuria is superadded it varies greatly in intensity and duration. It may be represented merely by a reddish discoloration or the urine may be almost black. The discoloration may be brief: only the urine voided during one night or in the early morning hours may exhibit it, the hemoglobinuria ceasing during that day. On the other hand, hemoglobinuria may continue for days or weeks on end, only to disappear until the onset of another paroxysm. The nocturnal appearance or exaggeration of the hemoglobinuria in some attacks was repeatedly commented upon while our 2 patients were under our care. Subsequently we discovered that many others had made the same observation. We have stated that Enckling was so impressed by the nocturnal rhythm of the hemoglobinuria that he expressed it in the title which he gave to the disorder. In the case of Rosenthal's patient, spontaneous hemoglobinuria disappeared in the last 4 years of his life. This patient illustrates the maximum duration of the disorder. Beginning at 19 the illness lasted 33 years, death ensuing a few hours after splenectomy had been performed.

Splenectomy accounted for 3 of the 8 deaths in the series of 22 cases. Removal of gall stones from the common duct was followed by a fatal issue in 1 case. One patient died suddenly of mesenteric thrombosis; while 1 succumbed to pneumonia and another to "grippe." Fourteen were alive from 1 to 12 years after the onset of the disease.

In addition to the characteristic symptoms and signs of chronic hemolytic anemia to which we have referred, there are some inconstant findings. Thus, the size of both the liver and spleen varies in different individuals, and in the same individual at different times.

Considering the persistent anemia it is not remarkable that venous thromboses are frequent. Both our patients suffered in the course of their illnesses from thrombosis of peripheral veins. Others have recorded the same process in the portal and intracranial vessels.

Examination of the blood reveals an anemia which may attain an extreme degree. The hemoglobin may fall as low as 15%; the

red blood cells, below a million. Reticulocytosis is almost constantly present with a marked elevation after one of the hemolytic crises. The mean corpuscular volume of the red blood cells in our 2 cases was normal or slightly increased. The cellular diameter corresponded approximately with the volume, so that there is no spherocytosis such as accompanies hemolytic icterus. Fragility of the erythrocytes is normal or slightly increased. The leukocytes may be normal in number but leukopenia is the rule during attacks; the count may be as low as 2000 with a relative lymphocytosis. The platelets are usually moderately decreased. Hemoglobinemia is constantly found. During the paroxysms bilirubinemia increases.

In these paroxysms the presence of varying amounts of hemoglobin in the urine is obvious to inspection. Its increase in the night specimens has already been stressed. Albuminuria and urobilinuria are constantly demonstrable. Marchiafava was the first to emphasize the presence of considerable hemosiderin in the centrifugate. Regarding it of great diagnostic importance it will be remembered that his designation for the disease reads "hemolytic anemia with perpetual hemosiderinuria." This iron-containing substance accounts for the yellowish-brown pigmentation of the casts, cellular elements and amorphous debris almost constantly detectable in the centrifugate.

A quantitative estimate of urobilin in the stools yields a high value.

IV.

Sufficient evidence has already been presented to differentiate chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria from other paroxysmal hemoglobinurias. Likewise, there are sufficient clinical data to separate the disorder from congenital or acquired hemolytic icterus. They include the absence of a hereditary factor, the infrequency of splenic enlargement, the therapeutic failure of splenectomy. Other differential diagnostic criteria are the inevitability of hemoglobinuria during the course of the fully developed illness in contrast with the extreme rarity of this sign in hemolytic jaundice, the normal or slightly increased fragility of the red blood cells and the absence of the spherocytosis characteristic of hemolytic icterus.

To bear in mind the remote possibility of favism as a cause of anemia, jaundice, fever and hemoglobinuria is sufficient to make inquiry as to the ingestion of the incriminating bean. Let it be likewise remembered that in this country the bean of the species *vicia fava* is used almost exclusively as pigeon food and cattle fodder. Finally, in discussing the differential diagnosis of the complaint under consideration, the acute hemolytic anemia of Lederer is also to be considered. The course of the disorder soon differentiates it from chronic hemolytic anemia. In Lederer's anemia transfusions

yield dramatic curative results, while if untreated, death usually follows. When recovery has occurred, there are no further paroxysms.

V.

The pathologic anatomic studies of the disorder under discussion are founded on 7 autopsies and the examination of 5 spleens removed at operation.

The studies yield evidence that this disorder can be differentiated on pathologic grounds as well as on clinical data from hemolytic icterus. While now and again as in life, the spleen was found somewhat enlarged, this enlargement was exceptional. Without exception, however, the note is made that the splenic pulp is not rich in red blood cells as in forms of hemolytic jaundice.

The tubular epithelium of the kidneys is filled with a yellowish-brown pigment which can be demonstrated to contain iron by the Prussian blue reaction. Neither the liver nor the spleen exhibits this hemosiderosis.

Gall stones, though suspected several times in life, were discovered only once, in contrast with their frequent occurrence in cases of hemolytic icterus. The bone marrow is hyperplastic.

VI.

From foregoing references to individual cases it may be concluded that chronic hemolytic anemia is compatible with life for many years. Half of the 8 deaths described in the literature followed surgical interventions. Until this syndrome received its proper nosologic status, splenectomy was performed on the assumption that the patients would receive the same benefit that accrued to those suffering from congenital or acquired hemolytic icterus. We have seen that in 8 of the 22 patients of the series the spleens were removed, and 3 died immediately after the operation. In only 1 of the 5 survivors, the patient of Donati,³⁴ was there an improvement that might be attributed to splenectomy. Marchiasava and Micheli have directed attention to a possible by-effect of the operation. While before splenectomy their patient tolerated transfusions badly; after the operation there seemed to be an immunity from reactions, an immunity which he lost toward the end of life. It must not be assumed that reactions invariably follow transfusions in this class of patients because both Giffin's²⁶ and Rosenthal's received blood without ill effect.

From the data just presented it follows that splenectomy is not indicated in the management of this group of patients. Transfusions are prone to be followed by untoward symptoms and a decision to introduce blood must be reached with this possibility in mind. Our first patient has never been transfused during the 10 years of her

disorder yet her hemoglobin which has been as low as 25% is at the time of writing 60%.

Other types of treatment were adopted by Hitzengerber.³⁵ In his patient the attacks of hemoglobinuria bore a close relation to the menstrual cycle. Therefore, in an attempt to modify the paroxysms irradiation of the ovaries was undertaken with the result that for 6 months there was neither a menstrual flow nor hemoglobinuria. However, the therapeutic effect was temporary. Three years later although amenorrhea had been reestablished, hemoglobinuria recurred and strange to say still in a monthly rhythm. Since the hemoglobin excretion was chiefly nocturnal Hitzengerber caused his patient to sleep at night in a room equipped with a "sun lamp." It is said that under these conditions the hemoglobinuria and the accompanying symptoms were greatly mitigated.

Analogy warrants the use of the measures employed in treating other forms of anemia. Hence, regulation of activities, appropriate diet, adequate doses of efficient iron preparations and the intramuscular injections of potent liver extracts are indicated.

VII.

Concerning the pathogenesis of the disease little information of value is available. Schally³⁹ stresses the significance of a chronic sinus infection associated with his patient's illness. He suggests that in some manner the long standing sepsis influences the bone marrow so that red blood cells of inferior quality are produced. These red cells are more susceptible to hemolysis, not, however, by virtue of any change in their osmotic resistance. Accordingly, the patient's red blood cells were hemolyzed *in vitro* by her own serum as well as by a normal individual's serum. We have been unable to confirm these observations.

The serum of Enneking's patient contained both auto- and iso-hemolysins. In our first patient's blood an autohemolysin was encountered during one of the attacks of hemoglobinuria, to disappear at the termination of the seizure.

The phenomenon of nocturnal exacerbation of hemoglobinuria is so striking and constant as to be almost pathognomonic of this particular disorder. Attempts to counteract some of the possible influences which may act as nocturnal stimuli to the production of hemoglobinuria have brought about incomplete alleviation in only one instance. Thus, it will be recalled that partial success accompanied continuous irradiation by means of a "sun lamp" in the case of Hitzengerber's patient. Iglauer³⁸ failed to influence any of the symptoms by feeding the patient liberally at night and by controlling the position in which he slept. We were unable to observe any inhibiting effect on the excretion of the hemoglobin by increasing the ingestion of liquids at night.

Based on some experiments of Bingold,⁴⁰ Schally emphasizes the possible importance of the absence of catalase from the hemoglobin containing urine. He suggests that catalase in the blood of these individuals may be inactivated so that its protective action over the integrity of the red blood cell is diminished.

A suggestive clue is supplied by Salén who reports that he overcame the nocturnal rhythm of hemoglobinuria in his patient by parenteral administration of typhoid vaccine or milk. Diurnal hemoglobinuria followed the experiments regularly. Salén ventures the opinion that his observations may justify the assumption that the hemolysis involved in this disorder may be caused by some sort of "chronic autointoxication." Perhaps this vague term may cover absorption of certain substances from the gastro-intestinal tract. An allergic agent could either be present originally in the food or else appear as an intermediary product of metabolism acting through a mechanism similar to that assumed to operate in favism. An alternative hypothesis postulates the absorption of a hemolysin arising from the same sources and entering the body by the same route. Neither of our patients showed evidence of hypersensitivity to any foodstuffs by the usual skin tests but additional information might be adduced by food elimination experiments. It is our impression that the most fruitful future investigations will proceed along such channels.

VIII.

Chronic hemolytic anemia of the type herein considered is admittedly a rare disease. However, in addition to the intrinsic value of distinguishing it from the conditions which it resembles, certain other conclusions emerge from the discussion. Above all, attention should be called to the fact that in the past, errors in diagnosis have led to unwise treatment. For instance, before the true nature of his ailment was recognized Salén's patient had been subjected to nephrotomy in a fruitless effort to discover the source of hematuria. The jaundice associated with the disorder has been misinterpreted and the mistake has led to misdirected operations on the gall bladder. It should be reiterated, too, that a confusion of the disease with hemolytic icterus has led to splenectomy, a serious operation of doubtful utility in chronic hemolytic anemia. Then, too, reactions following transfusions are so regularly encountered in patients suffering from the disorder that this procedure is certainly inadvisable.

Finally, it may be conjectured that the disease exists in a benign form and certain instances thus pass completely unrecognized. It has been pointed out that while hemoglobinuria is the most conspicuous and dramatic manifestation of the disorder, it is only by a fortuitous circumstance that it occurs. When hemolysis proceeds at a sufficiently slow pace, no gross hemoglobinuria may appear, a condition which may continue for years. Under these

circumstances a patient after having undergone the usual examinations, is found to be anemic or icteric and further search for an underlying hemolysis may be conceivably abandoned. Accordingly, it seems important to suggest that in all cases of anemia of obscure origin, the blood serum should be examined for hemoglobin. Or again, individuals who respond to the transfusion of blood with unexplained hemoglobinuric reactions should be subjected to closer scrutiny to determine whether they may not suffer from a latent form of the ailment. Only by an increased watchfulness will additional examples of chronic hemolytic anemia with paroxysmal nocturnal hemoglobinuria be discovered so that improper treatment will be avoided and eventually more logical methods of therapy be applied on the basis of an etiology yet to be determined.

Summary. Two new instances of an uncommon type of chronic hemolytic anemia associated with paroxysmal hemoglobinuria are herewith presented. The urinary discoloration occurs chiefly at night. Concomitant variable symptoms and signs of the syndrome are abdominal, lumbar and substernal pain, jaundice and fever. Features differentiating the disease from other paroxysmal hemoglobinurias, hemolytic anemias, and congenital hemolytic icterus are discussed. The chief blood changes are an anemia which may become profound, reticulocytosis and perpetual hemoglobinemia. The urine always contains urobilin and hemosiderin. Therapeutic measures are of little avail but the disease is compatible with life for many years. Splenectomy is a dangerous procedure, usually without benefit. Transfusions are generally followed by untoward reactions accompanied by hemoglobinuria. The theory is advanced that the malady may result from the absorption of some material from the gastro-intestinal tract acting as an allergen or a hemolysin. It is suggested that benign forms of this type of chronic hemolytic anemia may pass unrecognized when hemoglobinuria is not a conspicuous feature.

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COMPARATIVE STUDY OF CYTOPLASMIC AND NUCLEAR CHANGES IN NEUTROPHILS IN SEVERE INFECTIOUS STATES.

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THE literature on the hemogram in infection is voluminous and ever growing. In the past decade, the differential count according to the Schilling modification of Arneith's classification of neutrophils has become a routine procedure in many institutions. Numerous other simplifications of the Schilling count have been devised based on the increased formation and appearance of young neutrophils in the blood in response to an infecting agent. The value of the Schilling count is so unquestioned today that it should be regarded as indispensable in the study of infectious disease. It follows more

closely the course of the infection and presages in many instances oncoming complications with more accuracy than the total leukocyte count or the clinical impression. As infection progresses or complications occur there is an increase in the band forms and younger, immature neutrophils, often unrelated to the magnitude of the total white count. A steady rise in the band forms usually reflects extension of the infection, or pus formation. The appearance of still more immature forms, namely, myelocytes and myeloblasts, indicates an even graver state.

With but few exceptions, all the studies recorded in the literature on leukocytic changes in infection deal with nuclear changes, as recorded by the Schilling count or one of its modifications. Little attention has been devoted by contrast to the cytoplasmic alterations in neutrophils during disease states. However, since Mommensen¹ devised a staining technique which clearly and easily demonstrates these toxic or degenerative cytoplasmic changes in the neutrophils, more has been written about these important phenomena.

The degenerative changes in the peripheral neutrophil² consist essentially of an alteration of the staining quality of the cytoplasm, abnormal granulation, and vacuolization. With the Jenner-Giemsa stain as modified by Kugel and Rosenthal³ the cytoplasm is transformed from its normal eosinophilic pink to a dirty gray or blue color. This is usually accompanied by the appearance of toxic granules. The latter are coarse, irregular in distribution, stain deep blue, and are oxidase negative in contrast to the fine regularly distributed oxidase positive granules seen in the normal neutrophil. In some neutrophils the granules are so large that the cell may be mistaken for a basophil. In addition the cytoplasm may be vacuolated and present a moth-eaten appearance about the periphery, another evidence of toxicity. The presence of these three changes regardless of their degree is sufficient to classify a cell as toxic and warrant its inclusion in the calculation of the Degenerative Index. Kugel and Rosenthal³ have formulated a Degenerative Index based on these toxic changes in the cytoplasm as follows:

$$\text{Degenerative Index} = \frac{\text{Number of Degenerated Neutrophils}}{\text{Total Number of Neutrophil Cells}}$$

In a recent study² we enumerated the diseases in which toxic alterations of the cytoplasm of neutrophils appeared and did not appear; and the significance in diagnosis and prognosis their presence offered. In accord with other workers we found them most frequently present in severe spreading infections and sepsis; and that their greatest value lay in differentiating localized from generalized infections and in indicating development of complications. The conditions in which they occurred particularly were septicemia, bacteremia, pneumonia, peritonitis, osteomyelitis, and severe mastoid infections. From a prognostic viewpoint we were able to con-

firm Kugel and Rosenthal's observations that a high and rising Degenerative Index was usually indicative of a grave state.

The clinical importance of these toxic cytoplasmic changes in neutrophils is coming to be more appreciated; more data are accumulating concerning their presence and significance. Adler⁴ has shown that often more information can be gained by their study than by estimation of nuclear shifts. Prochnow⁵ states: "The hemogram in acute appendicitis is far more reliable if toxic granules are counted. The stain is not difficult and should be a routine measure. Toxic granules are the most important qualitative changes in leukocytes." Von Elsbach⁶ has reported that the appearance of toxic cytoplasmic changes, namely, granules and Döhle bodies in the hemogram in appendicitis, usually means purulent appendicitis. Harkins⁷ feels that a hemogram giving merely an estimate of the nuclear shift is incomplete and that to evaluate severe infections adequately, toxic cytoplasmic changes in the neutrophils should be included.

The literature is, moreover, particularly lacking in definite and exhaustive information regarding the comparative value of the cytoplasmic to the nuclear changes in neutrophils in severe infections. In the few such studies in the literature^{8,9} only general comparisons have been made. Since in severe infections the prognosis is a major consideration, and since opinions concerning it are usually based on the general clinical impression and estimation of the patient's state, it was thought worthwhile to investigate the aid which both the Schilling and toxic studies offered and to compare their relative qualities in this respect.

We therefore have studied patients suffering with severe infections (septicemia, bacteremia, pneumonia, peritonitis, osteomyelitis, and severe mastoiditis); diseases which we have found to be associated with both nuclear and cytoplasmic changes. Since it is generally appreciated that single hemograms are of but limited interpretative value, we made frequent examinations (total white counts, differentials, Schilling and Degenerative Indices), during the course of each illness, with repeated comparisons with the clinical state. From these studies we attempted to determine the value of each procedure independently and any advantage which one procedure might have over the other, *i. e.*, which of the indices—the Schilling or the Degenerative—was a more delicate and reliable measure of the disease state of the patient.

For the nuclear changes we employed Farley's¹⁰ filament non-filament modification of the Arneth-Schilling shift, in which neutrophils were divided into filament and non-filament cells, metamyelocytes and myelocytes. Farley regarded 9 non-filamented cells as an average normal and a count up to 16 non-filamented cells as the limit of the normal Schilling shift. Other authors have found higher limits of normality. Thus Love and Welter¹¹ found non-filament counts up to 25 as normal. Our findings essentially agree with

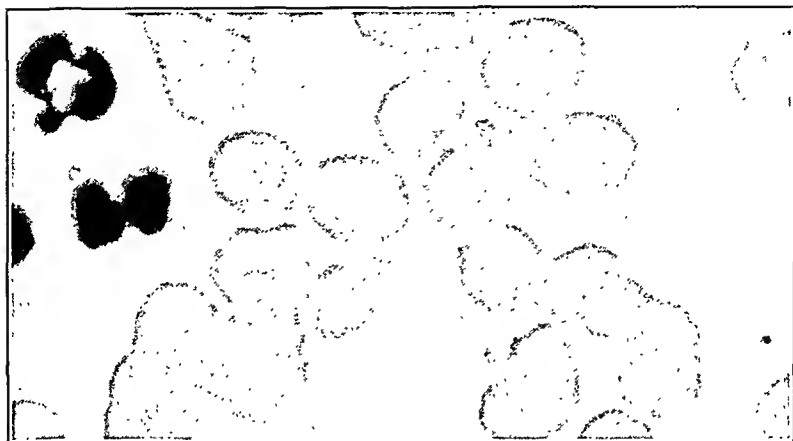


FIG. 1.—Blood smear showing cells without toxic granulation. From a case of rheumatic fever. ($\times 1500$.)

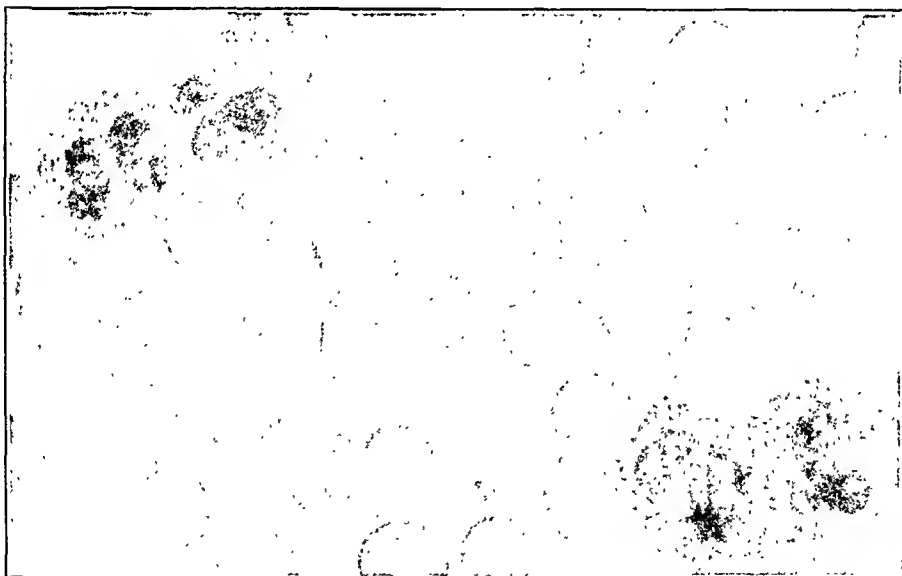


FIG. 2—Case 2. Blood smear showing cells with toxic granulations. From a fatal case of lobular pneumonia. Note all cells are toxic. ($\times 1500$.)

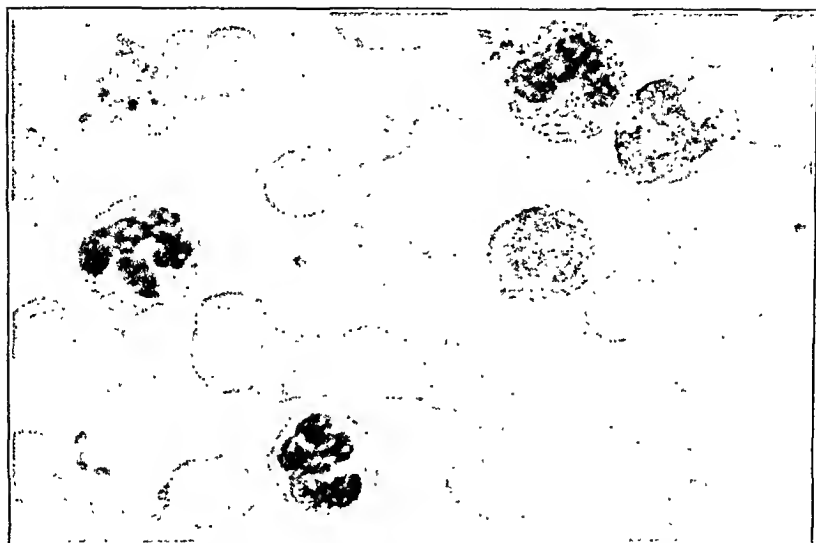


FIG. 3.—Case 16. Blood smear showing cells with some granulations. From a case of peritonitis which recovered. Note that four of the five cells are toxic. ($\times 1500$.)

Farley's and we have therefore used his more conservative figures. Weiss¹² analyzed 20,000 Schilling indices in infection and found that staff counts of 10 or above signified a moderate shift to the left, 33 staff cells a severe shift to the left, and 41 staff cells or above a very severe shift to the left. Crocker and Valentine¹³ studied 6000 hemograms in infection and found that nuclear shifts to the left of 50 cells or more are seen in the severe virulent infections in which prognosis is always guarded. In both Weiss, and Crocker and Valentine's series the severe and very severe shifts to the left were accompanied by toxic cytoplasmic changes but these were not compared with the nuclear changes. As their series of diseases demonstrating both nuclear shifts and toxic changes was essentially the same as ours, they offer a good comparison.

Based on these investigations and our experience we have looked upon non-filament counts of 8 to 16 as normal; counts of from 17 to 30 as a moderate shift to the left indicative of advancing infection; counts of 31 to 40 as a marked shift to the left and seen in severe infections; and counts of 41 or more as an extreme shift to the left seen in grave states.

For this study we classified the Degenerative Index similarly. Rosenthal and his co-workers have repeatedly shown that a persistent Degenerative Index of 90% or above usually spelled a fatal outcome, seen only in grave infections. In severe infections of lesser severity the Degenerative Index was correspondingly of a lesser magnitude. Sutro¹⁴ has graded the Degenerative Index in infections as follows: 1+, Degenerative Index up to 25%, seen in mild infections; 2+, up to 50%, in moderate infections; 3+, up to 75%, in severe infections; and 4+, up to 100%, in grave infections. From our previous work and the above investigations we feel that a 0 to 20% Degenerative Index may be accepted as normal or indicating a mild infection; 21 to 40% Degenerative Index a moderate infection; 41 to 70% a severe infection; and 71% or above a grave infection.

With these data, therefore, a comparison between these indices becomes possible. This we have done using the following numerical limits:

Schilling Index.	Degenerative Index, %.
8-16 Non-filamented cells; normal or mild infection (N) . . .	0-20
17-30 Non-filamented cells; moderate infection (M) . . .	21-40
31-40 Non-filamented cells; severe infection (S) . . .	41-70
41 plus Non-filamented cells; grave infection (G) . . .	71-100

For this investigation we studied the first 60 cases which fulfilled our criteria of severity. These were: 1, that the disease state was known to be associated with both toxic cytoplasmic and nuclear changes; 2, that the temperature had reached 102° F. or more; and 3, that the clinical courses were alarming by their severity. In these 60 cases simultaneous Schilling and Degenerative Indices were

performed periodically during the severe phases of their infections, and compared with each other and with the clinical states of the patients to attempt to determine which index proved to be a more accurate guide of the degree of the infection.

Present Study: Division of Cases. GROUP I—29 cases (48.3%). Cases in which both the Degenerative and Schilling Indices were both positive, but in which the Degenerative Index at all times was more informative, reflecting the clinical state with a greater degree of accuracy than the Schilling count.

1. *Illustrative Case.* A. S., female, aged 59, admitted on March 20, 1935, to the service of Dr. A. Trasoff, critically ill in state of diabetic coma with massive infection and spreading necrosis of deep tissues of upper half of right thigh. She had been drowsy for 48 hours at home as the infection was progressing, then lapsed into coma prior to admission. Catheterized specimen of urine was positive for sugar, acetone, and diacetic acid; blood sugar 484 mg. per 100 cc., and carbon dioxide combining power of blood 25 volumes %. Temperature averaged 102° F. Blood urea nitrogen, blood culture and Roentgen ray examination of the infected thigh were non-informative. On forced carbohydrate and fluid intake, adequate insulin, supportive measures, and wide incisions for drainage of the infected areas she temporarily rallied, the alkali reserve rose to 56, the acidosis disappeared, the blood sugar dropped to 155 mg. level, and the diabetic condition came under control. However, the infection could not be checked, she became more septic, and in spite of repeated blood transfusions, active medical and surgical treatment she expired on April 10th of advancing sepsis. Periodic examinations during the course of her septic state comparing Schilling and Degenerative Indices are as follows:

Hb. %	R.B.C. in millions.	W.B.C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I.	%
74	3.70	21.3	84	16	N	G	98
		18.0	54	28	14	4	M	G	100
82	4.05	20.8	62	20	10	8	M	G	95
		15.1	75	17	1	7	..	M	G	95
		17.9	28	56	2	1	12	1	G	G	100
87	4.42	19.4	58	32	8	2	S	G	100

F.—Filamented neutrophils; NF.—Non-filamented neutrophils; MM.—Metamyelocytes; M.—Myelocytes; E.—Eosinophils; B.—Basophils; S. I.—Schilling Index; D. I.—Degenerative Index.

GROUP II—20 cases (33½%). Cases in which the Degenerative and Schilling Indices were equal in merit; both at all times during the clinical course reflected the true state of the patient's illness.

1. *Illustrative Case.* L. R., negro male, aged 41, was admitted to the service of Dr. A. I. Rubenstone on May 11, 1935, desperately ill, septic and irrational, acidotic and dehydrated, temperature 104° F., pulse 120. and respirations 40 per minute. He had been well until 2 days before admission when dyspnea, fever, cyanosis, and hemoptysis occurred suddenly. There were signs of bilateral confluent lobular pneumonia. Urine was scanty, contained numerous casts, blood urea nitrogen was 68 mg., creatinin 2.8 mg., alkali reserve 52 volumes %, Wassermann Test positive. Sputum was negative for tubercle bacilli and positive for Pneumococcus Group IV. Spinal fluid examination yielded negative findings. Within 48 hours he developed areas of redness with cellulitis over arms and legs diagnosed erysipelas, and the blood culture taken on admission was now reported positive for hemolytic streptococcus. He remained septic, temperature ranged from 102° to

TABLE 1.—DATA OF GROUP I.

Case No.	Name.	Age (yrs.).	Diagnosis.	Number of examinations.	Clinical course.	Total leukocyte range 1000/cmm.	Comparative findings	Findings at most critical period of illness.
2	M. A.	3	Acute appendicitis Lobular pneumonia	6	Critically ill Septic course Temp. 102-105, expired	15.1 25.9	S. I. 0N-2M-3S-1G D. I. 0N-0M-0S-6G	L. 23,200 D. I. 97% (G) S. I. 56F-40NF-1MM-1M (G)
3	I. R.	47	Lobar pneumonia	3	Critical; temp. 104, expired	18.7 17.5	S. I. 0N-3M D. I. 0N-1M-1S-1G	L. 17,500 D. I. 63% (S) S. I. 57F-27NF (M)
4	B. F.	2	Lobar pneumonia Mastoiditis Lateral sinus thrombosis	27	Septic, toxic course; temp range 100-105	18.5 16.2	S. I. 17N-6M-2S-2G D. I. 11N-5M-9S-2G	L. 15,100 D. I. 71% (G) S. I. 32F-28NF (M)
5	A. H.	40	Lobar pneumonia	4	Toxic; sustained temp. 104	17.9 10.9	S. I. 2N-1M-0S-1G D. I. 0N-1M-0S-3G	L. 13,900 D. I. 73% (G) S. I. 45F-31NF-1MM (S)
6	M. M.	33	Lobar pneumonia	5	Toxic; sustained temp. 105	21.4 19.4	S. I. 1N-4M D. I. 1N-1M-3S	L. 21,200 D. I. 67% (S) S. I. 58F-28NF (M)
7	I. H.	17	Lobular pneumonia	7	Toxic; temp. 103	23.9 10.3	S. I. 5N-1M-1S D. I. 3N-1M-2S-1G	L. 23,900 D. I. 85% (G) S. I. 53F-41NF (G)
8	I. B.	45	Lobar pneumonia	5	Toxic; sustained temp. 105	26.0 9.1	S. I. 3N-1M-0S-1G D. I. 1N-1M-0S-3G	L. 26,000 D. I. 100% (G) S. I. 67F-24NF-5MM-2M (S)
9	J. W.	1	Lobular pneumonia	14	Septic, temp. 100-105 daily	24.6 10.7	S. I. 11N-3M D. I. 3N-5M-3S-3G	L. 10,700 D. I. 64% (S) S. I. 50F-8NF-1MM (N)
10	F. B.	37	Lobular pneumonia	9	Toxic, septic; temp. 100-103	18.3 6.4	S. I. 4N-2M-1S-2G D. I. 1N-3M-2S-3G	L. 16,400 D. I. 95% (G) S. I. 49F-37NF-4MM (G)
11	E. C.	28	Lobar pneumonia	8	Toxic; sustained temp. 104	20.8 9.4	S. I. 2N-4M-1S-1G D. I. 2N-0M-0S-6G	L. 11,400 D. I. 100% (G) S. I. 62F-28NF (M)
12	S. S.	7	Massive suppuration and cellulitis of thigh	7	Septic, temp. 100-104 daily	20.6 12.1	S. I. 1N-3M-1S-2G D. I. 0N-1M-3S-3G	L. 20,600 D. I. 80% (G) S. I. 32F-50NF (G)
13	F. S.	35	Pelvic peritonitis	11	Septic, temp. 102	21.2 11.3	S. I. 7N-3M-1S D. I. 4N-2M-5S	L. 21,200 D. I. 58% (S) S. I. 60F-22NF (M)
14	E. M.	5	Retropharyngeal abscess	9	Septic, temp. 104 daily	24.8 7.5	S. I. 6N-3M D. I. 3N-6M	L. 14,200 D. I. 40% (M) S. I. 49F-16NF (N)
15	B. S.	19	Purulent perinephritis	6	Toxic, septic; temp. 103	29.7 16.2	S. I. 4N-2M D. I. 0N-4M-1S-1G	L. 18,700 D. I. 86% (G) S. I. 70F-10NF (N)
16	A. H.	55	Staphylococcal septicycemia	9	Critical, septic, temp. 100-105 daily expired.	16.2 36.4	S. I. 0N-6M-2S-1G D. I. 0N-1M-3S-5G	L. 16,100 D. I. 85% (G) S. I. 38F-52NF-1MM (G)
17	T. T.	26	Erysipelas, streptococemia	8	Critical, septic, temp. 99-105 daily	15.2 10.2	S. I. 3N-5M D. I. 3N-1M-4S	L. 13,900 D. I. 77% (G) S. I. 58F-15NF (N)
18	A. H.	34	Infected pulmonary infarction secondary to pelvic cellulitis	6	Septic, toxic temp. 99-104	17.5 8.1	S. I. 3N-3M D. I. 2N-0M-4S	L. 17,500 D. I. 52% (S) S. I. 59F-26NF (M)
19	E. B.	26	Lobar pneumonia	4	Toxic, temp. 104	18.3 12.8	S. I. 0N-1M-2S-1G D. I. 0N-0M-3S-1G	L. 17,900 D. I. 90% (G) S. I. 59F-34NF-1MM (S)
20	J. R.	22	Lobar pneumonia	8	Toxic, temp. 102	19.2 7.6	S. I. 3N-3M-1S-1G D. I. 1N-1M-4S-2G	L. 19,200 D. I. 68% (S) S. I. 42F-54NF-1M (G)
21	E. D.	27	Metritis following Cesarean section	6	Toxic, temp. 99-102 daily	20.3 12.8	S. I. 3N-2M-1S D. I. 0N-3M-1S-2G	L. 18,500 D. I. 63% (S) S. I. 59F-25NF-1MM (M)
22	J. C.	8	Mastoiditis	9	Toxic, temp. 101-105 daily	21.4 9.8	S. I. 5N-3M-1S D. I. 1N-0M-7S-1G	L. 21,400 D. I. 67% (S) S. I. 40F-31NF (S)
23	E. S.	11	Mastoiditis	13	Toxic, temp. 100-105 daily	27.4 14.8	S. I. 7N-4M-2S D. I. 2N-5M-2S-2G	L. 21,100 D. I. 57% (S) S. I. 50F-22NF (M)
24	J. B.	2	Massive infection secondary to multiple body burns	7	Toxic, septic; temp. 100-106	30.0 8.4	S. I. 4N-3M D. I. 1N-0M-3S-3G	L. 12.1 D. I. 90% (G) S. I. 54F-28NF (M)
25	C. F.	26	Pelvic peritonitis	14	Septic, toxic; temp. 99-102	26.2 12.1	S. I. 5N-9M D. I. 0N-0M-1S-13G	L. 20.8 D. I. 94% (G) S. I. 68F-18NF (M)
26	J. L.	8	Lobular pneumonia, empyema, otitis media	23	Toxic, septic; temp. 101-105	27.9 10.4	S. I. 9N-8M-2S-4G D. I. 1N-3M-7S-12G	L. 23,900 D. I. 100% (G) S. I. 45F-40NF-4MM (G)
27	S. L.	10	Staphylococcal septicycemia	9	Critical, septic; temp. 104-106, expired	14.6 22.2	S. I. 1N-2M-3S-3G D. I. 1N-1M-1S-6G	L. 20,200 D. I. 100% (G) S. I. 55F-28NF-0MM-4M (S)
28	L. L.	37	Lobular pneumonia	6	Toxic, septic; temp. 102-104	16.6 9.7	S. I. 2N-3M-1S D. I. 1N-3M-0S-2G	L. 14,800 D. I. 81% (G) S. I. 62F-26NF (M)
29	W. M.	4	Lobular pneumonia, mastoiditis	7	Septic, toxic; temp. 100-105	53.2 11.4	S. I. 4N-1M-1S-1G D. I. 0N-0M-4S-3G	L. 31,400 D. I. 90% (G) S. I. 35F-42NF-2MM (G)

105° F., and in spite of antistreptococcic serum, repeated blood transfusions, chemotherapy, and supportive measures he expired 5½ days after admission. The blood examinations done during his period of hospitalization are as follows:

Hb. %	R. B. C. in millions.	W. B. C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I.	%
90	4.50	21.4	39	50	4	7	..	G	G	80
83	4.22	21.9	38	40	5	1	13	3	G	G	83
86	4.12	16.6	23	45	11	1	16	4	G	G	87

TABLE 2.—DATA OF GROUP II.

Case No.	Name.	Age (yrs.).	Diagnosis.	Number of examinations.	Clinical course.	Total leukocyte range 1000/c.mm.	Comparative findings.	Findings at most critical period of illness.
2	L. G.	55	Lobular pneumonia	5	Septic, toxic; temp. 102; expired	27.1 28.9	S. I. 0N-1M-3S-1G D. I. 0N-1M-2S-2G	L. 20,600 D. I. 77% (G) S. I. 40F-38NF-2MM-1M (G)
3	H. N.	21	Lobar pneumonia	9	Toxic; sustained temp. 104	11.0 9.1	S. I. 3N-2M-3S-1G D. I. 2N-2M-4S-1G	L. 8,400 D. I. 90% (G) S. I. 42F-34NF (S)
4	M. R.	51	Lobular pneumonia; toxic hepatitis	13	Septic, toxic; temp. 103	25.6 8.5	S. I. 5N-3M-4S-1G D. I. 4N-5M-2S-2G	L. 12,800 D. I. 72% (G) S. I. 45F-31NF-1MM (S)
5	J. H.	40	Lobular pneumonia	5	Septic, toxic; sustained temp. 105	60.4 7.6	S. I. 2N-0M-1S-2G D. I. 1N-0M-1S-3G	L. 60,400 D. I. 100% (G) S. I. 38F-34NF-9MM-0M (G)
6	C. H.	46	Lobar pneumonia empyema	8	Toxic; temp. 103-105	22.5 13.5	S. I. 4N-4M D. I. 5N-1M-2S	L. 22,500 D. I. 58% (S) S. I. 68F-21NF (M)
7	I. F.	42	Lobular pneumonia	3	Toxic; temp. 104	9.2 8.1	S. I. 1N-1M-1S D. I. 1N-1M-1S	L. 9,200 D. I. 49% (S) S. I. 54F-26NF (M)
8	J. G.	3	Lobular pneumonia; mastoiditis	5	Septic, toxic; temp. 105-106	42.4 9.8	S. I. 2N-0M-2S-1G D. I. 2N-0M-1S-2G	L. 42,400 D. I. 71% (G) S. I. 62F-22NF (M)
9	S. S.	3	Lobar pneumonia	5	Toxic; temp. 105	27.4 11.3	S. I. 0N-3M-0S-2G D. I. 0N-1M-1S-3G	L. 10,200 D. I. 90% (G) S. I. 26F-18NF-4MM-10M (S)
10	I. E.	50	Lobular pneumonia; toxic psychosis	6	Septic; temp. 99-103	5.4 9.7	S. I. 5N-1M D. I. 4N-1M-1S	L. 9,700 D. I. 48% (M) S. I. 44F-21NF (M)
11	M. S.	38	Lobular pneumonia	9	Toxic; temp. 105	19.3 12.2	S. I. 4N-4M-1S D. I. 5N-2M-2S	L. 15,300 D. I. 82% (G) S. I. 59F-15NF (N)
12	M. S.	23	Lobar pneumonia	7	Toxic; temp. 103; sustained	28.0 12.9	S. I. 2N-3M-2S D. I. 3N-2M-2S	L. 15,000 D. I. 51% (S) S. I. 50F-21NF (M)
13	H. S.	19	Staphylococcic septiciopyemia	21	Critical; septic; temp. 100-102; expired	17.4 24.9	S. I. 0N-4M-13S-7G D. I. 0N-0M-0S-15G	L. 17,500 D. I. 100% (G) S. I. 32F-59NF-7MM-1M (G)
14	C. S.	45	Osteomyelitis	7	Toxic, septic; temp. 103	27.4 10.4	S. I. 1N-4M-2S D. I. 1N-2M-2S-2G	L. 27,400 D. I. 83% (G) S. I. 68F-26NF (M)
15	S. L.	27	Pelvic peritonitis	19	Septic; temp. 102	20.0 8.5	S. I. 8N-4M-0S-7G D. I. 3N-4M-6S-6G	L. 15,500 D. I. 71% (G) S. I. 32F-50NF-1MM (G)
16	A. W.	14	Generalized peritonitis secondary to ruptured appendicitis	14	Toxic, septic; temp. 99-101	22.7 6.3	S. I. 5N-4M-3S-2G D. I. 4N-1M-4S-2G	L. 16,700 D. I. 74% (G) S. I. 50F-31NF-1MM (S)
17	E. K.	47	Generalized peritonitis secondary to ruptured appendicitis; lobular pneumonia	6	Septic, toxic; temp. 100-101	20.8 10.4	S. I. 0N-4M-1S-1G D. I. 1N-3M-0S-2G	L. 20,800 D. I. 89% (G) S. I. 50F-22NF (M)
18	M. F.	4	Generalized peritonitis secondary to ruptured appendicitis	7	Septic, toxic; temp. 102	23.2 11.3	S. I. 0N-1M-2S-1G D. I. 0N-1M-1S-5G	L. 14,800 D. I. 95% (G) S. I. 39F-42NF-2MM-1M (G)
19	H. F.	2	Mastoiditis	5	Toxic; temp. 102	17.1 10.2	S. I. 3N-2M D. I. 3N-1M-1S	L. 17,100 D. I. 61% (S) S. I. 52F-21NF (M)
20	M. B.	28	Suppurative metritis	4	Toxic; temp. 102	18.1 12.4	S. I. 0N-3M-0S-1G D. I. 0N-2M-2S-0G	L. 12,400 D. I. 65% (S) S. I. 52F-21NF (M)

GROUP III—7 cases (11.7%). Cases in which the Degenerative Index alone was positive and reflected the clinical state of the patient, the Schilling Index being of no value.

1. *Illustrative Case.* L. B., female child, aged 5 years, admitted to the service of Dr. B. Lipschutz in August, 1933, in state of severe shock due to extensive body burns involving an area covering the entire anterior surface of the body reaching from the chin and face to the symphysis pubis, from posterior axillary line of one side to posterior axillary line of the other. There were also additional burns of back and extremities. She was treated locally with tannic acid solution, and generally with repeated blood transfusions, venoclysis, and supportive measures. Over half the body surface was involved with second and third degree burns; infection set in with toxemia and sepsis, the child became weaker and more debilitated, temperature fluctuated from 100°–105° F. daily, and she expired in September, 1934, more than 1 year after admission. Blood examinations made at weekly intervals during her most septic state prior to exitus are as follows:

Hb. %	R.B.C. in millions.	W.B.C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I. %
81	4.00	21.7	38	37	2	1	21	1	S	G 75
		21.5	42	32	..	1	..	3	21	1	S	G 88
		20.8	55	19	1	18	7	M	G 84
78	3.94	18.4	59	21	15	5	M	G 79
		20.5	63	16	19	2	N	G 87
		14.4	45	28	21	6	M	G 100
77	3.75	33.4	64	26	9	1	M	G 91

TABLE 3.—DATA OF GROUP III.

Case No.	Name.	Age (yrs.).	Diagnosis.	Number of examinations.	Clinical course.	Total leukocyte range 1000/c.mm.	Comparative findings.	Findings at most critical period of illness.
2	L. G.	22	Lobar pneumonia; pneumococemia; empyema	8	Toxic, septic; temp. 101–103	20.2 10.4	S. I. 7N-1M D. I. 0N-0M-1S-7G	L. 20,200 D. I. 76% (G) S. I. 44F-21NF (M)
3	A. D.	5	Lobular pneumonia	4	Critical; toxic; expired; temp. 104	13.9 21.2	S. I. 3N-1M D. I. 0N-0M-0S-4G	L. 16,900 D. I. 87% (G) S. I. 46F-21NF (M)
4	M. B.	4	Lobular pneumonia; mastoiditis	5	Toxic, septic; temp. 99–103	21.4 14.5	S. I. 5N D. I. 0N-1M-4S	L. 21,400 D. I. 75% (G) S. I. 32F-14NF (N)
5	M. M.	27	Septic metritis; pelvic peritonitis	9	Toxic, septic; temp. 100–105	26.5 9.1	S. I. 8N-1M D. I. 4N-3M-2S	L. 25,600 D. I. 40% (M) S. I. 72F-16NF (N)
6	A. S.	31	Septic abortion; peritonitis	6	Toxic, septic; temp. 100–106	14.9 8.1	S. I. 5N-1M D. I. 1N-4M-1S	L. 14,200 D. I. 60% (S) S. I. 71F-12NF (N)
7	F. J.	22	Retropharyngeal abscess	5	Toxic; temp. 100–103	21.4 9.8	S. I. 5N D. I. 2N-2M-1S	L. 12,600 D. I. 64% (S) S. I. 47F-12NF (N)

GROUP IV—3 cases (5%). Cases in which both the Degenerative and the Schilling Indices were positive, but in which the Schilling Index at all times was more informative, reflecting the clinical state with a greater degree of accuracy than the Degenerative Index.

1. *Illustrative Case.* W. C., sthenic, white male, aged 44, referred by Dr. J. Levy, was admitted to the hospital on April 28, 1935, acutely ill, complaining of cough, pain in the chest, and expectoration of 1 day's duration. Temperature was 103° F. Consolidation of the left upper lobe was diagnosed and confirmed by Roentgen ray examination. Blood chemistry, culture, and serology were normal. Sputum examination yielded Pneumococcus Group IV and was negative for tubercle bacillus. Temperature ranged from 101° to 105° F., then dropped to normal on the 7th day, rose to 100° for a few days, reached normal and remained there. Although he presented the usual toxicity for lobar pneumonia, his clinical course was favorable throughout, and he was discharged 3 weeks after admission as cured. Blood examinations taken periodically during the severe stage of his illness disclosed the following:

Hb. %	R.B.C. in millions.	W.B.C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I. %
100.	5.17	29.6	42	52	4	2	..	G	N 20
		28.2	42	47	2	8	1	G	S 41
		15.3	41	37	4	..	2	..	16	..	G	S 57
95	5.10	15.1	56	14	..	1	2	..	22	5	N	S 46
		31.4	30	50	4	14	2	G	S 67
		32.0	35	53	3	1	8	..	G	S 60
		14.6	39	21	4	2	3	..	27	4	M	S 45
105	5.20	10.4	36	20	2	..	4	..	32	6	M	N 18
		10.2	49	5	1	40	5	N	N 7

TABLE 4.—DATA OF GROUP IV.

Case No.	Name.	Age (yrs.).	Diagnosis.	Number of examinations.	Clinical course.	Total leukocyte range 1000/c.mm.	Comparative findings.	Findings at most critical period of illness.
2	J. A.	55	Lobular pneumonia	2	Septic; critical; temp. 104; expired	18.9 15.4	S. I. 0N-0M-0S-2G D. I. 0N-0M-2S-0G	L. 15,500 D. I. 65% (S) S. I. 15F-55NF-14MM-2M (G)
3	I. K.	6	Lobar pneumonia mastoiditis; empyema	4	Septic; critical; temp. 105-107; expired	16.0 6.2	S. I. 0N-0M-0S-4G D. I. 1N-1M-1S-1G	L. 6,200 D. I. 91% (G) S. I. 17F-39NF-1MM-1M (G)

GROUP V—1 case (1.7%). Cases in which the Schilling Index alone was positive and reflected the clinical state of the patient, the Degenerative Index being practically of no value.

1. *Illustrative Case.* S. A., female, aged 25, admitted to the service of Dr. Moses Behrend on February 23, 1934, for nausea, vomiting, fever, and pain in right lower abdomen of 5 days' duration. Temperature was 101° F. Patient was toxic and dehydrated, urine showed +2 acetone. Diagnosis of peritonitis secondary to ruptured appendicitis was made, the abdomen opened, gangrenous ruptured appendix removed, and the peritoneal cavity drained. The postoperative course was stormy, complicated by ileus and the development of a pelvic abscess necessitating rectal incision for drainage. Temperature ranged between 101° and 102° F. daily. Several blood transfusions were given. Finally drainage decreased, clinical condition improved, temperature reached normal on the 28th day, and she was discharged cured.

on the 35th day following admission. Blood examinations during the course of her septic state are as follows:

Hb. %	R.B.C. in millions.	W.B.C.	F.	NF.	MM.	M.	E.	B.	Lym.	Mon.	S. I.	D. I.	%
85	4.45	25.9	70	18	10	2	M	N	0
		21.2	58	28	1	1	10	2	M	N	10
		20.4	59	28	1	10	2	M	S	50
		25.8	45	38	1	2	13	1	G	N	17
81	4.20	19.3	44	32	22	2	S	N	0
		10.9	53	30	15	2	M	N	12
		15.0	56	8	32	4	N	N	6
88	4.50	11.8	68	12	2	..	16	2	N	N	0

The following table represents the compared Indices of the entire series of the 60 cases at the most critical period of the patients' illnesses:

	Normal.	Moderate.	Severe.	Grave.
Schilling Index	9	23	11	17
Degenerative Index	1	3	18	38

Discussion. From this study it would appear that in severe infections, serial estimations of the degenerative cytoplasmic changes in neutrophils, as expressed by the Degenerative Index, are a more reliable and accurate guide of the severity and prognosis of the illness than estimations of nuclear changes, as expressed by the Schilling Index. This is shown in diseases presenting both nuclear and cytoplasmic changes namely, the severe toxic states encountered in septicemia, bacteremia, pneumonia, peritonitis, osteomyelitis, and severe mastoiditis. In the advanced stages of infection the polymorphonuclear neutrophils show the greatest degree of cytoplasmic and nuclear changes, and therefore, such disease states offer the best basis for the comparison of the values of these two findings. We have shown in our previous work that mild infectious states, as rheumatic fever, arthritis, tuberculosis, etc., usually do not present cytoplasmic degenerative changes whereas the Schilling shift may or may not be marked. Such diseases, therefore, do not offer themselves for a comparative study. Hence it is evident that the results of our study are applicable only to severe infectious states and may not hold for relatively milder disease states.

In general, the results of this study may be summarized as follows: In these extremely septic states, while the Schilling count was of value and a good index of the patient's clinical condition, it was not as valuable or as accurate and reliable as the Degenerative Index in the majority of cases. In 20 cases of the 60 studied (Group II) both the Degenerative and Schilling Indices were equally valuable. Of the remaining 40 cases, in 36 (90%) (Groups I and III), the Degenerative Index was superior to the Schilling Index; whereas in the other 4 cases (10%) (Groups IV and V), the Schilling Index was superior to the Degenerative Index. We also noted in the course of our serial examinations that the degenerative cytoplasmic changes

appeared earlier in the illness and persisted longer throughout the course than did the corresponding nuclear changes. Again, at the height of the diseases studied, during the most critical days of the patients' illnesses, a single examination comparing the two tests found the Degenerative Index to be superior; it denoted 38 grave states as compared to 17 by the Schilling Index, and 18 severe states as compared to 11 by the Schilling Index.

Conclusions. 1. Sixty cases of severe infectious diseases have been studied to compare the relative value clinically of the degenerative cytoplasmic changes (Degenerative Index) and the nuclear changes (Schilling Index) in polymorphonuclear neutrophils.

2. In 20 of the 60 cases studied both the Degenerative Index and Schilling Index proved to be of equal value.

3. Of the remaining 40 cases, in 36 (90%) the Degenerative Index was superior to the Schilling Index. In only 4 of these 40 cases (10%) was the Schilling Index superior to the Degenerative Index.

4. This series showed that at the height of the illness the Degenerative Index more accurately reflected the existing clinical state and the subsequent course.

5. Degenerative cytoplasmic changes appeared earlier, and persisted longer than did the corresponding nuclear changes during the critical stages of the illnesses studied.

6. It is important to note how valuable both tests proved to be, and that though the Degenerative Index proved to be superior in the majority of cases, the Schilling Index again showed itself to be a very valuable procedure.

7. From this study it is again evident that no hemogram in severe infection is complete without determination of the Degenerative Index.

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CHRONIC CONSTRICTIVE PERICARDITIS, ELECTROCARDIOGRAPHIC AND CLINICAL STUDIES.

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CHRONIC constrictive pericarditis has been known as a clinical entity since the early descriptions by Widenmann¹ and Kussmaul.² Pick³ described the condition in the following words: "There is a symptom complex characterized by circulatory disturbances, enlarged liver and ascites, caused by latent pericarditis." This symptom complex has been known by his name for many years. The clinical features are characterized by high venous pressure, lowered arterial pressure with a low pulse pressure, pulsus paradoxus (first described by Widenmann¹), ascites and enlarged liver. There is little cardiac enlargement. Broadbent's sign and systolic retraction of the lower sternum or the left lower chest are rarely observed. The electrocardiogram may be an additional aid in establishing the diagnosis of this condition. Eleven cases of constrictive pericarditis with low voltage curves have been reported: Sprague and White,⁴ 1; Willius and Killins,⁵ 2; Turner,⁶ 1; Waldorp,⁷ 1; Burwell and Strayhorn,⁸ 1; and White⁹ reports 5 cases with low voltage and 10 with abnormalities in the T waves.

The following observations were made upon 11 patients with the clinical diagnosis of chronic increased intrapericardial pressure. Pericardiectomy was performed on all of these patients by Dr. C. S. Beek,¹⁰ who has reported case histories of 6 of the patients referred to in this paper. Microscopic examination of the resected pericardium in all instances showed the parietal and visceral layers to be fused and indistinguishable, with densely fibrous and hyalinized tissue which was poorly vascularized. Occasional small collections of lymphocytes were observed. Some of the cases showed focal

TABLE 1.—VOLTAGE OF ELECTROCARDIOGRAMS OF 11 CASES.

Date.	P, mm.	Q, mm.	R, mm.	S, mm.	T, mm.	Axis shift.
Case 1. 9/20/29 11/21/29 12/24/29	F. I., ♂, aged 13 yrs. +1.5(II)† Pericardectomy +1.75(II)	-1(III) -3(III)	+5.5(III) +12(II)	-0.75(II) -3(I)	Isoelectric Iso.(I) -1(II) -5(III) +1(I) -0.5(II) -1.5(III) +1.3(I) +2.5(II) -1.5(III)	0 0 0 0
3/19/30	+1.5(II)	-4(III)	+12.5(II)	-4.5(I)		
3/ 3/34	+2(II)	-3.5(II)	+25(II)	-4.5(I)		
Case 2. 4/17/31 8/ 8/31	J. V., ♂, aged 30 yrs. +1.5(II) Pericardectomy	-1(III)	+5.5(II)	-1(I)	-0.5(I) -0.5(II) Iso.(III)	
Case 3. 11/20/31 11/25/31	M. F., ♀, aged 23 yrs. +1.75(I, II) Pericardectomy	...	+5(II)	-0.5(III)	Isoelectric 0.5(II) Iso.(III)	0
Case 4. 1/25/33 2/2/33 4/13/33 4/13/34 8/22/35	L. M., ♀, aged 32 yrs. +1.5(I) Pericardectomy +1.5(I) +1.5(I) +1.5(I) -0.5(III) -0.5(III)	+3(II) +2(II) +4(I) +3(I)	-2.25(II) -1.25(II) -2(I) -2(I)	+1(I) +0.5(II) -1(III) +1(I) Iso.(II) -1(III) +1.5(I) +0.5(II) -1.5(III) +1.5(I) +0.5(II) -1.5(III)	0 Slight. 0
Case 5. 7/19/33 7/31/33 8/11/33 4/14/34 8/23/34	G. R., ♂, aged 28 yrs. +1(I) Pericardectomy +1(I, II) +1.5(I) +1.5(I)	-0.5(I) -0.25(I) -0.5(I) -1(I)	+5(II) +4(II) +2.5(II) +4.5(III)	-1.5(I) -2.5(II) -2(II) -2(I)	-0.5(I) -1.5(II) -1(III) +0.75(I) -1(II) -0.5(III) -0.5(I) -1(II) -0.5(III) Diph. ±0.5 -1(II) -0.5(III)	Slight. 0
Case 6. 3/12/34 4/ 7/34 4/ 7/34 6/21/34 6/24/35	G. B., ♂, aged 25 yrs. Auricular fibrillation Auricular fibrillation Pericardectomy Auricular fibrillation Auricular fibrillation	+7(II) +5(II) +6(II) +9(II)	-3(II) -3(II) -2(II) -2.5(II)	-0.5(I) -1(II) -0.5(III) -1(I) -1(II) Iso.(III) Iso.(I) Iso.(II) Iso.(III) +1.0(I) Iso.(II) -1.5(III)	0 Definite.
Case 7. 5/17/34	M. Z., ♀, aged 37 yrs. Auricular fibrillation Pericardectomy	...	+4.5(II)	-0.5(I)	-0.5(I) -0.5(II) Iso.(III)	Slight.
Case 8. 8/ 3/34	L. C., ♂, aged 15 yrs. +1.5(II) Pericardectomy	-5(IV)	+7(II)	...	+1(I) +0.5(II) -0.5(III)	0

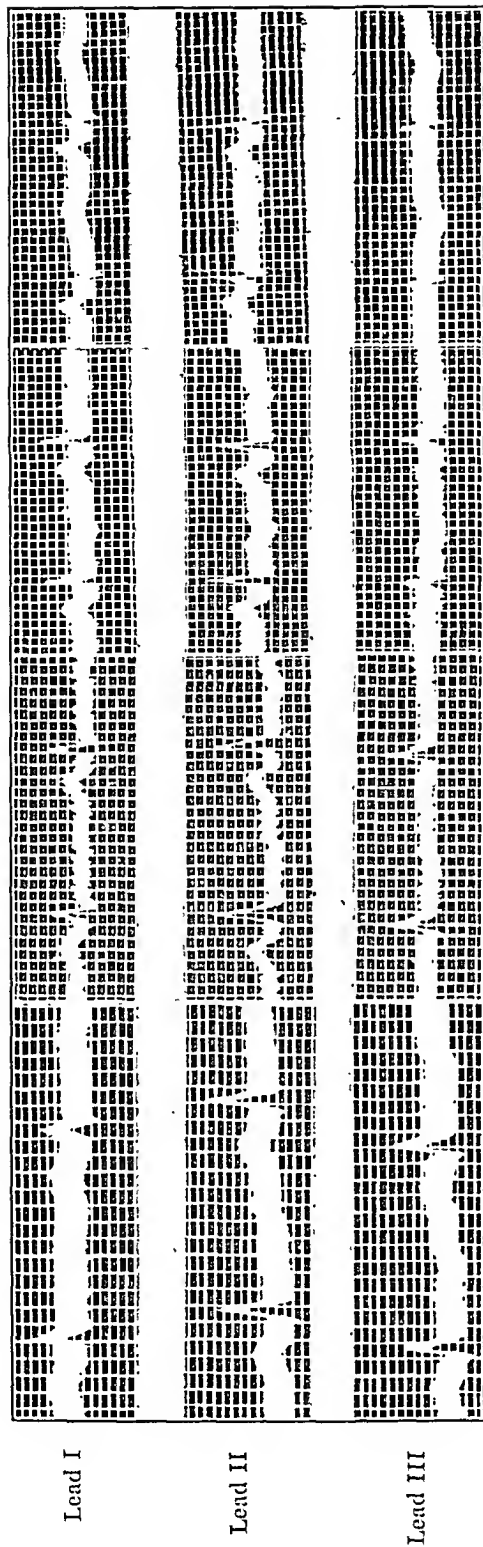
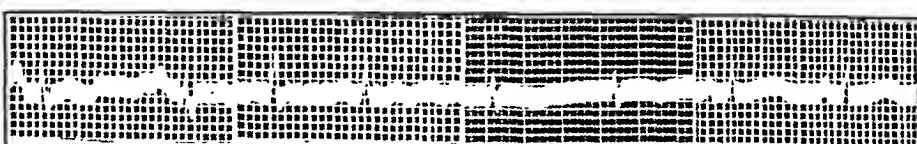


FIG. 1.—Electrocardiograms of Cases 1 to 4, before operation.

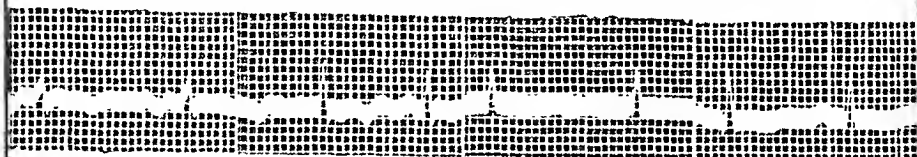
Lead I



Lead II



Lead III

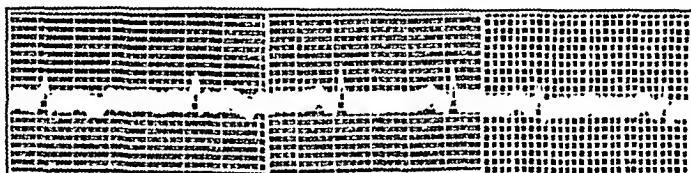


Lead IV

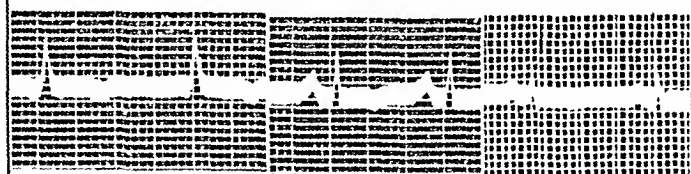


Case 5 6 7 8
Fig. 2.—Electrocardiograms of Cases 5 to 8, before operation. Lead IV: apex—left leg.

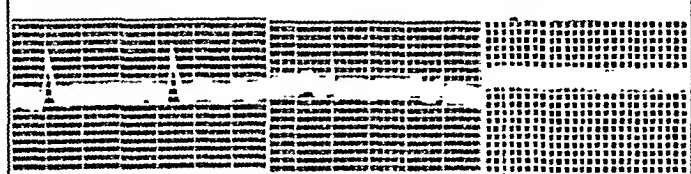
Lead I



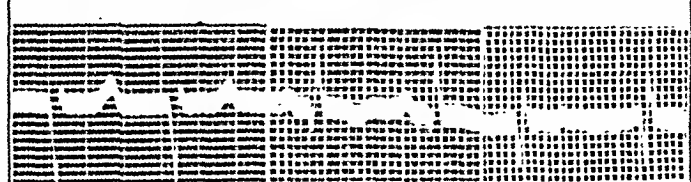
Lead II



Lead III



Lead IV



Case 9 10 11
Fig. 3.—Electrocardiograms of Cases 9 to 11, before operation.

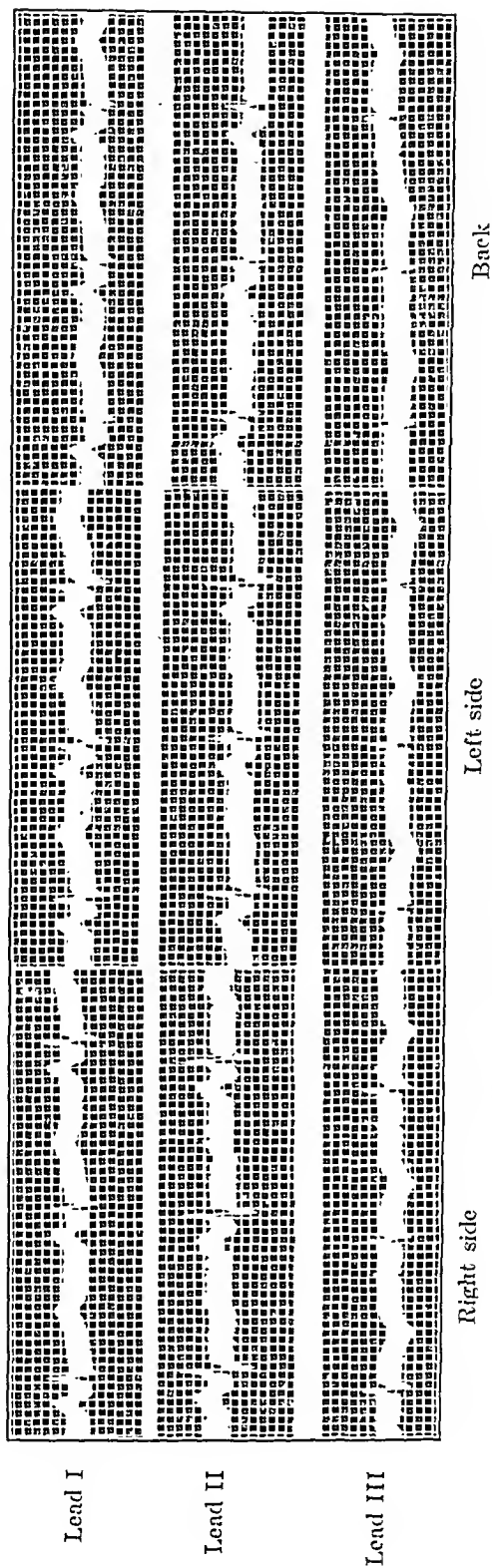
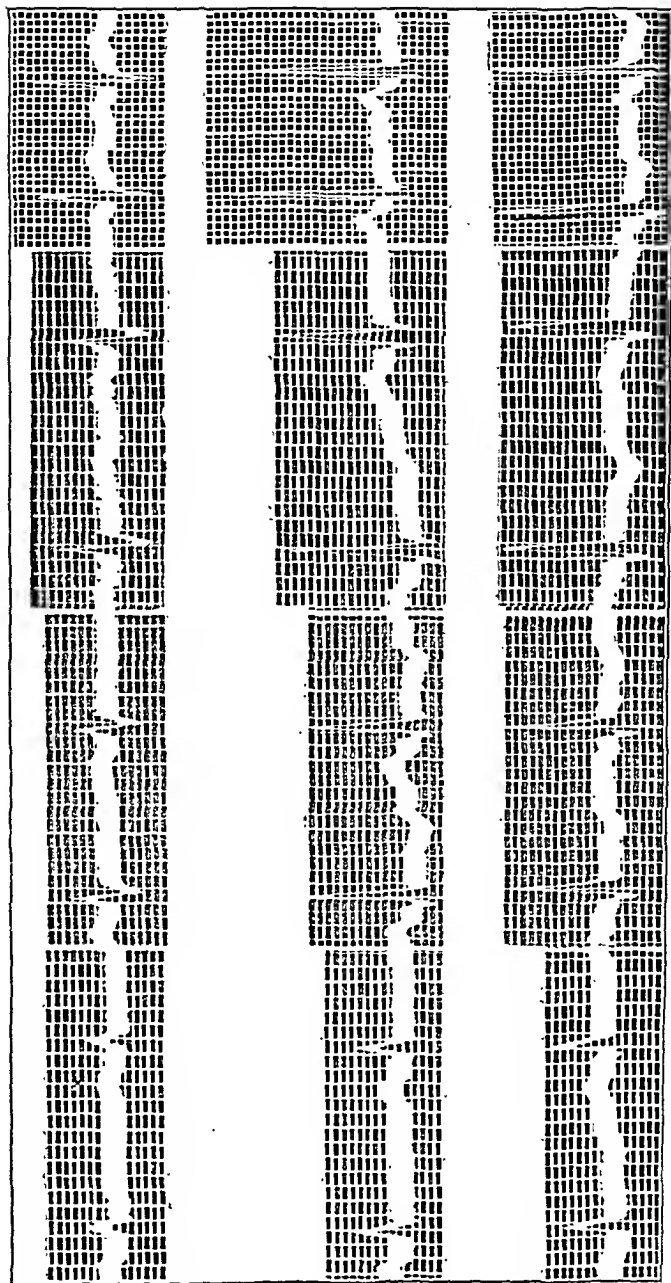


FIG. 4.—Showing unchanging electrical axis (Case 4).



September 20, 1929

December 24, 1929

March 19, 1930

March 2, 1934

Fig. 5.—Progressive increase in voltage, following operation (Case 1).

TABLE 1.—VOLTAGE OF ELECTROCARDIOGRAMS OF 11 CASES.—*Continued.*

Date.	P, mm.	Q, mm.	R, mm.	S, mm.	T, mm.	Axis shift.
Case 9. 2/17/33 4/13/34 4/17/34	B. S., ♀, aged 57 yrs. Auricular flutter Auricular flutter Auricular fibrillation	+7(III) +4.25(II) +4.5(II)	-1.5(I) -0.5(I) ...	+0.5(I) +1(II) -0.5(III) -0.5(I) -1(II) -0.5(III)	Slight.
11/ 8/34	Auricular fibrillation	...	+5(II)	-1(I)	-0.5(I) -1.25(II) -0.25(III) -0.5(I) -1(II) -0.5(III)	
11/10/34 11/26/34	Pericardectomy Auricular fibrillation	-0.5(III)	+5(II)	-1.5(I)	-0.5(I) -1.25(II) -0.25(III) -0.5(I) -1(II) -0.5(III)	
12/20/34	Auricular fibrillation	-0.5(III)	+7(II)	...	-0.5(I) -1(II) -0.5(III)	
4/ 3/35	Auricular fibrillation	-0.5(III)	+10(III)	...	-0.5(I) -1.5(II) -0.25(III)	0
Case 10. 10/ 3/33	I. L., ♂, aged 30 yrs. +1.5(II)	...	+7(II)	...	-1(I) +1.5(II) +0.5(III) +0.5(I) -0.5(II) -0.25(III)	0
12/ 1/34	+1.5(II)	-0.5(I)	+5(II)	-0.5(III)	-0.5(I) -0.5(II) -0.25(III)	0
1/15/35 1/31/35	Pericardectomy +1.5(II)	-0.5(I)	+6(II)	...	-0.5(I) -0.5(II) -0.25(III)	0
12/10/35	+2.25(II)	-0.5(I)	+7(II)	-0.5(III)	-0.5(I) -1.0(II) -0.5(III)	0
Case 11. 4/ 3/35	V. P., ♂, aged 46 yrs. +1(II)	...	+2(II)	-0.5(II)	+0.5(I) -0.5(II) Iso. (III)	0
4/10/35 6/25/35	Pericardectomy +1(II)	...	+3.5(I)	-2(I)	-0.25(II) -0.5(II) -0.25(III)	0

† Indicates lead with highest voltage.

areas of calcification. There were no changes that could be construed as characteristic of rheumatic or tuberculous infection.

Electrocardiographic studies were made in all cases. Certain features were common to all of the records: Voltage of the *Q-R-S* complex below the usual limits of normal;* slurring of the *Q-R-S* in all leads; and *T* waves of low amplitude, either of positive or of negative sign. The presence of *P* waves of normal voltage was an interesting finding (Figs. 1, 2 and 3). In 7 of the cases, change of position did not appreciably affect the electrical axis (Fig. 4), and only changed it slightly in 3 cases. In 1 case the test was not made.

The chest lead showed a *Q* wave in all cases and in only 1 case was an *S* wave observed. The *T* wave was upright in 5 of the 7 cases.

In Table 1 are listed the electrocardiographic observations in the 11 cases.

* Significance of voltage: The normal electrocardiogram is the resultant of electrical effects originated in the heart and conducted by the body tissues to the electrodes on the extremities. The resultant maximum voltage (in any one recorded lead) is a small fraction of the total voltage in direct leads from the heart. The latter figure has a value of approximately 20 times that of the conventional electrocardiogram.

Table 2 shows the details of the chest lead which was placed in the fourth interspace just lateral to the sternum.

TABLE 2.—LEAD IV* IN 7 CASES.

Date.		P, mm.	Q, mm.	R, mm.	S, mm.	T, mm.
Case 5. 7/19/33	G. R., ♂, aged 28 yrs.	Isoelec- tric				
7/31/33	Pericardectomy		-3.0	+4.5	...	+1.5
9/23/33		-0.5	+1.5	...	+0.5
8/23/34		-0.5	+4.25	...	+1.0
Case 6. 3/12/34	G. B., ♂, aged 25 yrs. Auricular fibrillation	...	-8.5	+4.0	...	+2.0
4/ 7/34	Pericardectomy	...				
6/21/34	Auricular fibrillation	...	-6.0	+5.5	...	-1.0† +2.0†
6/24/35	Auricular fibrillation	...	-6.0	+6.5	...	-2.0
Case 7. 5/17/34	M. S., ♀, aged 37 yrs. Auricular fibrillation	...	-3.5	+1.0
Case 8. 8/ 3/34	E. C., ♂, aged 15 yrs.	+0.5	-5.5	-1.25
Case 9. 4/13/34	B. S., ♀, aged 57 yrs. Auricular flutter	...	-14.0	+2.0	...	Upright.
11/10/34	Pericardectomy	...				
4/ 3/35	Auricular fibrillation	...	-5.0	+24.0	-2.0	+3.5
Case 10. 10/ 3/33	I. L., ♂, aged 30 yrs.	+0.5	-13.0	+5.0	...	+3.0
12/ 1/34	Diphasic ±0.5	-7.5	+1.0	...	-0.5
1/15/35	Pericardectomy	Diphasic	...	+1.0	-10.0	+1.5
12/10/35					
Case 11. 4/ 3/35	V. P., ♂, aged 46 yrs.	-0.5	-5.0	+4.5	...	-2.5
4/10/35	Pericardectomy					
6/25/35	-0.25	-5.5	+7.25	...	+4.0

* Lead IV. Chest electrode in fourth interspace to left of sternum. Indifferent electrode on left leg.

† Varying.

Following operation 4 cases (1, 6, 9, 11) showed an increase in voltage. There was no change in the P or T waves.

Electrocardiograms were taken during the operative procedure on 4 patients. There were surprisingly few changes to be observed.* Ventricular extrasystoles were noted in 3 of the 4 cases when the pericardium was being dissected from the heart. There was a transient change in mechanism in 3 patients, shifting pacemaker

* Kurtz, C. M., Bennett, J. M., and Shapiro, H. H., *J. Am. Med. Assn.*, 106, 431, 1936, report similar electrocardiographic changes during surgical anesthesia.

being noted twice and nodal rhythm once. There was slight elevation of the *S-T* interval in the first and second leads during operation in 2 cases, but this had disappeared by the time the procedure was completed. The details of the changes observed, the blood pressure readings and the rate are listed in Table 3:

TABLE 3.—CHANGES OBSERVED DURING OPERATION.

Case No.	Start of operation.	Mediastinum opened.	Heart bulging through pericardium.	Heart freed of pericardium.	End of operation.
Case 8 E. C.	Rate, 124-156; shifting pacemaker Blood pressure, 104/70	Rate, 142; normal mechanism Blood pressure, 115/70	...	Rate, 144; rare ventricular extrasystoles; lower voltage; <i>S</i> and <i>T</i> waves sl. elevated Blood pressure, 125/70	Rate, 138; occasional ventricular extrasystoles; voltage still lower.
Case 9 B. S.	Rate, 122 Blood pressure, 120/100	Rate, 136 Blood pressure, 105/75	Rate, 136 Blood pressure, 125/80	Rate, 112 Blood pressure, 130/80	Rate, 150; very slight decrease in voltage. Blood pressure, 130/90
Case 10 I. L.	Rate, 152 Blood pressure, 123/82	Rate, 128; voltage slightly increased Blood pressure, 145/90	Rate, 136; occasional ventricular extrasystoles; shifting pacemaker Blood pressure, 115/90	Rate, 124; shifting pacemaker Blood pressure, 116/80	Rate, 136; normal mechanism. Blood pressure, 105/70
Case 11 V. P.	Rate, 96	Rate, 111; nodal rhythm	Rate, 121; nodal rhythm; ventricular extrasystoles; elevated <i>S</i> and <i>T</i> waves in Leads I and II	Rate, 116; normal mechanism; <i>S</i> and <i>T</i> ₂ isoelectric; <i>S</i> and <i>T</i> waves sl. elevated; occasional ventricular extrasystoles	Rate, 98; nodal rhythm; <i>S</i> and <i>T</i> waves in Leads I and II isoelectric.

Table 4 shows in tabular form the clinical findings on the 7 cases that recovered from the operative procedure:

TABLE 4.—CIRCULATORY TESTS BEFORE AND AFTER OPERATION.

Case No.	Pre-operative.				Interval since operation.	Postoperative.			
	Blood pressure.	Venous pressure, cm.	Vital capacity, %.	Cardiac output, %.		Blood pressure.	Venous pressure, cm.	Vital capacity, %.	Cardiac output, %.
1	90/70	35	55	...	4½ yrs.	128/78	3.5	80	-12.3
4	90/72	25	60	-42.3	14 mos.	118/72	..	81	-39.0
5	96/74	27	52	-50.4	9 "	110/70	18.0	82	-37.0
6	100/80	28	68	-28.6	14 "	112/78	17.0	..	-3.2
9	104/90	32	58	-41.0	5 "	120/70	18.0	69	-28.0
10	105/85	35	40	-25.0	4 "	110/75	19.0	..	-9.5
11	110/70	25	36	-36.4	2½ "	120/70	13.0	47	-17.7

Blood pressure is in millimeters of mercury. The venous pressure is in centimeters of physiologic solution of sodium chlorid. The vital capacity is in percentage of estimated normal. Cardiac output is by Grollman's acetylene method in percentage.

Dieuaide¹¹ noted that change in the position of patients with adhesive pericarditis from one lateral position to the other is not followed by the normal change in the electrical axis of the heart, seen most prominently in Leads I and III of the electrocardiogram. In normal individuals, there is usually a significant shift of the electrical axis; and in patients with rheumatic heart disease, there is usually a considerable shift. In Dieuaide's series, 12 patients came to necropsy. These included 8 with clinical signs suggestive of adhesive pericarditis, 4 of whom had a relatively fixed electrical axis, and all showed lesions of the pericardium and of the mediastinum. Pathologic findings in the pericardium and mediastinum were lacking in the other autopsied cases. In the 3 patients with fixation of the electrical axis in Dieuaide's series (Cases 5, 6 and 7), the maximum voltage of $Q-R-S$ was 22, 14 and 18 mm., respectively; *i. e.*, voltage above the normal figure. The first of these patients had syphilitic heart disease and the other 2 rheumatic heart disease. The large voltage in these cases agrees with our findings in rheumatic heart disease and serves to differentiate the latter condition from non-rheumatic adhesive mediastinopericarditis.

Electrocardiograms from 100 cases of rheumatic heart disease at Lakeside Hospital were reviewed, of which cases 21 came to necropsy. Table 5 is a summary of the findings in these cases.

TABLE 5.—ELECTROCARDIOGRAPHIC VOLTAGE IN 100 CASES OF RHEUMATIC HEART DISEASE.

	No. of cases.	Age range.	Maximum voltage range.	Average maximum voltage.*
Cases with active infection (rheumatic or subacute bacterial)	31	14-39	7-43	15.8
Cases with congestive failure	30	13-63	4.5-28	12.5
Cases with heart disease an incidental finding	39	7-66	7-31	15.6
Average of all cases	14.6

* In Lewis¹² series of 52 normal medical students, the variations in the height of the largest wave of $Q-R-S$ were from 5.5 to 16.5 mm., with an average of 11 mm. In Pardee's¹³ series of 26 normal college students, the voltage varied from 8 to 23.5 mm. Pardee concluded that from these 78 normal records, the minimum value should be 7 mm. and the maximum value 17 mm. In Hallaran and Shipley's¹⁴ series of 200 normal individuals between 20 and 35 years of age, the average voltage for men was 12.4 mm., varying from 19.2 to 5.8 mm. (3 men had voltage below 7 mm; their voltage was 6.7, 5.8 and 5.8 mm.). The 100 women had an average voltage of 10.8 mm., varying between 19.7 and 3.6 mm. (There were 11 women with voltages below 7 mm. and 4 below 6 mm. The lowest voltage was in a woman who had a basal metabolic rate of -14.)

This increase in voltage of the $Q-R-S$ complex is found in the cases of active infection as well as in the group without evidence of active infection or of congestive failure. In the cases of congestive failure, the voltage range was from 4.5 to 28 mm., with an average voltage of 12.5 mm., slightly less than the average in the remaining cases. In only 1 case was low voltage found (4.5 mm.) and the

necropsy of this case revealed extensive mediastinopericardial adhesions and severe myocardial scarring. In the 100 cases the voltage was 7 mm. or less in 6 instances. Of these, 3 had congestive failure, 1 subacute bacterial endocarditis, 1 acute rheumatic fever, and in 1 case the cardiac lesion was incidental.

The low amplitude of the *Q-R-S* complex and of the *T* waves in these cases of adhesive mediastinopericarditis could be explained by severe myocardial damage or by change in the tissues immediately surrounding the heart (dense adhesions, hydropericardium, hydrothorax and ascites). Severe myocardial damage as a cause of low amplitude is difficult to reconcile with the practically complete clinical recovery in Case 1 (Fig. 5), the increased voltage in 4 of the cases recovering from operation, and the absence of myocardial involvement as shown by histologic examination in Cases 3, 5 and 7. The absence of low voltage in curves recorded from cases of rheumatic heart disease with advanced congestive failure suggests that changes in conduction remote from the heart do not entirely explain the low voltage. Conditions immediately surrounding the heart, such as fluid or dense adhesions, do reduce the amplitude of the electrocardiogram. This reduction in voltage was seen in the experimentally produced pericardial effusion of Katz, Scott and Feil.¹⁵ Likewise Wilson,¹⁶ in his experimental work, showed that "any increase in the conductivity of the body tissues, particularly of those tissues which lie in close proximity to the heart, will decrease the amplitude of the electrocardiographic deflections. The question arises, then, as to whether edema of the lungs, pericardial effusion, hydrothorax, ascites, or massive edema of all the body tissues may not decrease the amplitude of the electrocardiographic deflections." In 1 of the cases of rheumatic heart disease coming to necropsy, previously mentioned in this paper, the maximum voltage was 4.5 mm. This case showed dense, pericardial adhesions extending out into the mediastinum. One of the patients with hemopericardium and 1 with pyopericardium reported by Scott, Feil and Katz¹⁷ showed monophasic curves of normal voltage.

It is suggested that the low voltage curves seen in our series of 11 cases of chronic increased pericardial pressure (all of whom were without evidence of vascular disease) were due to the dense adhesions surrounding the heart. Low voltage also occurs with myocardial fibrosis secondary to the narrowing of the lumen of the coronary vessels, and occurs with myxedema.¹⁸ The characteristic clinical pictures are of aid in the differentiation of these latter conditions.

Summary. Eleven patients with adhesive mediastinopericarditis, upon whom pericardectomy was performed, all had electrocardiograms with *Q-R-S* complexes of low amplitude. The *T* waves were low in voltage. Following pericardectomy the *Q-R-S* voltage increased in 4 of 7 cases.

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COMPLETE AURICULO-VENTRICULAR DISSOCIATION.

A CLINICAL STUDY OF SEVENTY-TWO CASES WITH A NOTE ON A CURIOUS FORM OF AURICULAR ARRHYTHMIA FREQUENTLY OBSERVED.

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THIS report deals with certain clinical features of a group of 72 patients who, on at least one occasion, revealed complete auriculo-ventricular dissociation; it is designed to supplement and extend the observations published in 1923 by White and Viko.¹ Recently

Ellis² reported 43 cases of complete heart block analyzed from a point of view somewhat like that we have employed in this paper.

Although complete *A-V* block may be suspected from clinical observations, objective registration representing auricular and ventricular contractions is necessary for final proof. This proof was obtained electrocardiographically in each of our 72 cases. The rare instances of complete *A-V* dissociation, occasioned by the automatic capacity of some lower center exceeding that of the normal pacemaker, have not been included.

Consideration of the Group as a Whole. Of the 72 patients there were exactly twice as many males as females (Table 1). The age incidence was overwhelmingly greatest in the later decades of life although instances occurred in the entire range from infancy to very old age.

TABLE 1.—NUMERICAL AND SEX DISTRIBUTION OF CASES ACCORDING TO THE PROBABLE ETIOLOGY OF THE *A-V* BLOCK TOGETHER WITH THE AVERAGE AGE OF EACH GROUP.

	Male and female.		Male.		Female.	
	No.	Average age.	No.	Average age.	No.	Average age.
Probably etiology of <i>A-V</i> block.						
Coronary heart disease . . .	47	63.0	36	62.6	11	63.4
Congenital heart disease . . .	4	5.7	1	0.3	3	7.5
?Congenital heart disease . . .	2	22.5	2	22.5
Rheumatic heart disease . . .	3	41.6	2	45.5	1	34.0
Luetic heart disease . . .	3	42.6	3	42.6
?Diphtheritic heart disease . .	4	34.7	1	28.0	3	37.0
Rheumatic, luetic or coronary heart disease	1	48.0	1	48.0
Coronary or luetic heart disease	2	46.0	2	46.0
Coronary or rheumatic heart disease	4	50.7	2	55.5	2	46.0
Entirely uncertain	2	34.5	2	34.5
Total	72	52.6	48	56.7	24	44.5

The probable etiological factors were congenital defects in 6, diphtheria in 4, rheumatic fever in 3, syphilis in 3, and arteriosclerotic coronary disease in 47; in the remaining 9 either the causal factor was unknown or multiple factors were present.

At the time complete *A-V* block was first proven in 66 of our 72 cases, the average duration of cardiac symptoms was 2 years and 9 months. The functional cardiac status was as follows: 7 had normal cardiac reserve, 11 a slight decrease, 31 a moderate decrease, 11 a marked decrease, and 6 had frank congestive failure. Attacks of dizziness, syncope or convulsions, symptoms related to the block itself, were present in about $\frac{2}{3}$ of the patients; measures directed toward the relief of these symptoms were largely unsuccessful. Digitalis was given to 20 patients; it was of significant value in relieving heart failure in 4, notwithstanding the slow ventricular rates.

The ventricular rates, obtained from the initial electrocardiograms showing complete *A-V* block, ranged from 19 to 71 a minute and averaged 40; in 17 instances there was more than 5% variation in the time between the slowest and fastest rates. Partial or complete bundle branch block was present in 48 of the 72 electrocardiograms, auricular fibrillation in only 2, auricular standstill in 1, and premature ventricular beats in 10.

We were able to obtain subsequent information, at least in regard to life or death, in 68 of the 72 cases. The average duration of life after the initial record showing complete *A-V* block, in 41 patients dying of cardiovascular disease, was 2 years and 2 months; in 8 dying of some affection other than heart disease, 6 years and 8 months; in 17 remaining alive, 6 years and 11 months.

There is little to be gained in studying these cases as a single group since the heart disease responsible for the block usually affects the clinical course, treatment, and prognosis more than does the block itself. Because of this they have been grouped with regard to etiological considerations.

Coronary Heart Disease and Complete A-V Block. This group comprises 47 cases in which coronary heart disease was quite certainly the cause of the heart block; arterial hypertension was an associated finding in 25 of the 47.

The males outnumbered the females more than 3:1; there were 36 of the former and 11 of the latter.

The average age at which complete *A-V* block was first proven was the same for both sexes, 62 years. The extremes in age were 47 and 85 years. There were 5 patients in the fifth decade of life, 12 in the sixth, 19 in the seventh, 9 in the eighth, and 2 in the ninth.

The average duration of symptoms before the discovery of complete *A-V* block was 2 years and 8 months and was nearly twice as long in the females as in the males. At the time complete *A-V* block was first proven an evaluation of the degree of heart failure was made in 43 of the 47 cases. In only 1 of these was the cardiac reserve considered normal, in 5 it was slightly decreased, in 20 moderately decreased, in 11 markedly decreased, and in 6 there was frank congestive failure.

Coronary thrombosis was responsible for the onset, simultaneously, of cardiac symptoms and complete *A-V* block in 6 patients, in 3 of whom it was fatal; 1 additional patient suffered a fatal attack of coronary thrombosis after the discovery of the conduction defect. Angina pectoris was present in 9 patients at the time block was first discovered and developed after the onset of block in one other.

In addition to the usual symptoms of cardiac weakness 32 of the 43 patients, concerning whom the data were complete, suffered attacks caused presumably by cerebral anemia; 11 had dizzy spells, 20 had syncopal attacks, and 1 had syncope with convulsions. Three patients experienced only one attack of dizziness or syncope

while the remaining 29 suffered many attacks. Such attacks heralded the onset of cardiac symptoms in 8 patients, while in 4 they were the probable cause of death.

Arterial blood pressure, in 40 of the 47 cases, averaged 173 mm. Hg systolic and 83 mm. Hg diastolic. In 24 of the 25 with coronary and hypertensive heart disease the average pressure was 203 mm. Hg systolic and 88 mm. Hg diastolic, while in 16 patients with coronary disease without hypertension the average pressures were 128 mm. Hg systolic and 74 mm. Hg diastolic. There was no substantial difference in pressures between the sexes. Only occasionally were low diastolic pressures recorded. The lowest was 50 mm. Hg and the accompanying systolic pressure was 140; aortic regurgitation was not present in that case.

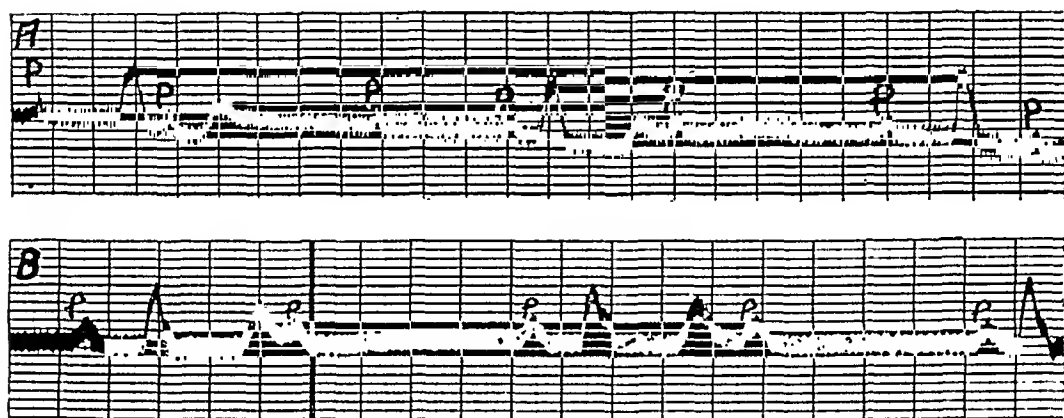


FIG. 1.—A shows a lengthening of the second auricular cycle while the third cycle is similar in duration to the first. The fourth auricular cycle is longer than the first or third, and may be due to the early occurrence of the ventricular contraction in this cycle. B shows a less marked example of auricular arrhythmia.

The initial electrocardiograms showing complete *A-V* block were analyzed. The average ventricular rate was 38 a minute; the extremes were 20 and 64; in 8 instances there was more than 5% variation in the time between the slowest and fastest ventricular rates. The average auricular rate was 86. There was little or no correlation between auricular and ventricular rates. In 35 of the 47 electrocardiograms there was partial or complete bundle-branch block; auricular fibrillation occurred in 2 instances, auricular standstill in 1, and ectopic ventricular beats in 10.

Subsequent electrocardiograms were taken in 25 cases; in 16 the *A-V* block remained complete, in 5 there was a return to partial *A-V* block, and in 4 the *A-V* conduction time returned to normal.

The treatment of patients in this group was directed chiefly toward the failing heart muscle and followed the usual plan. Digitalis was given and its effect noted in 16 patients; in 3 it was appreciably beneficial while in 13 it was not.

Treatment designed to increase the heart rate or to abolish the

cardiocerebral (Adams-Stokes) attacks was attempted with 30 patients. Adrenalin was given to 2 patients with good effect, its use being limited by the inconvenience of administration and short-lived action. Ephedrin, given to 7 was beneficial in 3, without benefit in 3, and in 1 it caused troublesome palpitation. Thyroid extract was given to 7 patients with questionable benefit to 1. Barium chlorid ($\frac{1}{2}$ to 1 gr. t.i.d.) was used in 8 cases without benefit to any. Atropin was given to 6 patients without benefiting any. In 1 patient a slight fever caused the pulse rate to increase from 40 to 60 where it remained for a period of 5 days after the temperature returned to normal. In a few patients the avoidance of certain things which sometimes precipitated attacks constituted the best treatment.

The average duration of life, in 45 of the 47 cases, after complete *A-V* block was recognized, was as follows: 1 year and 7 months in the 30 cases dying of cardiovascular disease; 6 years in the 6 cases dying of various other causes; and 3 years and 10 months to date in the 9 cases remaining alive. The longest duration of life was 16 years and 5 months; in 12 instances the duration of life was over 4 years, while in 18 it was less than 1 year.

The causes of death in the 30 cases dying of cardiovascular disease were listed as follows: congestive heart failure in 4, Adams-Stokes attacks in 4, coronary thrombosis in 4, cerebral accident in 2, "sudden death" in 7, and "heart disease" in 9.

Congenital Heart Disease and Complete A-V Block. There were 4 cases, 1 male and 3 female, in which the heart block was assuredly of congenital origin. The average age was 5 years and 8 months. None had had diphtheria, rheumatic fever, congenital lues, or scarlet fever. The heart was slightly enlarged in 2 cases. Patency of the interventricular septum was questioned in 3, but the classical signs of such a defect were not present. It is important to note that there was no other definite evidence of congenital heart disease save the complete *A-V* block. If these cases had been first seen in later life the etiology would be uncertain or possibly wrongly ascribed to some other factor. Cardiac reserve was normal in 3 cases and slightly decreased in 1. None had had dizzy spells or syncopal attacks.

The electrocardiograms showed an average ventricular rate of 59, the extremes being 49 and 71; the average auricular rate was 130. In 2 instances there was marked variation between the slowest and fastest ventricular rates. In addition to complete *A-V* block the electrocardiogram in 1 instance (an infant of 9 months) showed inversion of *T* in Lead I, and in one other, partial bundle-branch block.

We have been unable to trace 2 patients, lack of cardiac symptoms probably being responsible for their losing touch with the

clinic. The cardiac status of the remaining 2 has not changed over periods of 1 year, and 7 years and 9 months respectively.

Two additional patients probably belong to this group. Both were female, 1 aged 12 years and the other 31. Neither had had diphtheria, rheumatic fever, syphilis, or scarlet fever. Both had been free from dizzy spells and syncopal attacks. The older patient had slight cardiac enlargement and slight dyspnea, while the younger had no cardiac symptoms and a normal sized heart. The cardiac status remains unchanged after 4 years and 4 months in the case of the older patient, and 18 years and 6 months in the case of the younger.

Rheumatic Heart Disease and Complete A-V Block. There were 2 men and 1 woman in whom the probable cause of complete A-V block was rheumatic heart disease. One of the men, aged 48, had a normal sized heart. He had no symptoms whatever and the electrocardiogram, in addition to complete A-V block, showed at times block of the ventricular pacemaker.³ Later his heart enlarged and attacks of dizziness, and symptoms of heart failure appeared in moderate degree. He died following an operation 17 years after the onset of block which always remained complete. Necropsy revealed mitral stenosis; the coronary arteries were freely patent. No detailed postmortem studies of the conductive system were made.

The other man, aged 43, had a markedly enlarged heart with aortic and mitral stenosis without congestive failure. For 1 week he had had many severe attacks of dizziness, syncope, and convulsions. He contracted bronchopneumonia and died 3 days after the discovery of block. Necropsy was not performed.

The 1 woman in this group, aged 34, had a slightly enlarged heart with mitral stenosis and aortic regurgitation. She had had cardiac symptoms for 11 years and syncopal attacks for 1 month. An electrocardiogram showed low voltage in addition to complete A-V block. She was observed over a period of 2 years and 6 months during which time her cardiac status remained about the same and the block remained complete. Further efforts to trace this patient have failed.

Luetic Heart Disease and Complete A-V Block. Three male patients with an average age of 43 years comprise this group. They all complained of cardiac symptoms and the cardiac reserve was moderately decreased in each. One had angina pectoris and 1 other had syncopal attacks. All had moderately enlarged hearts, and one had aortic regurgitation. Their blood pressures averaged 133 mm. Hg systolic and 55 mm. Hg diastolic. The Wassermann reaction was positive in 2 and the third showed luetic cardiovascular changes at necropsy. No detailed postmortem studies of the conductive system were made. In addition to complete A-V block the initial electrocardiograms showed in each case partial or complete

bundle branch block also, in 1, retrograde auricular responses, and in 1 other, a block of the ventricular pacemaker. One patient who received inadequate antiluetic treatment died of heart failure in 8 months. The remaining 2 cases received prolonged antiluetic therapy. The block remained complete in 1 but there was a return to normal rhythm in the other with partial bundle branch block remaining. Both were quite well and worked hard for years. One died suddenly 7 years and 10 months after the discovery of the block and necropsy revealed luetic aortitis with marked narrowing of the first portions of the coronary arteries. The other died of "heart disease" 4 years after the discovery of the block.

Diphtheritic Heart Disease and Complete A-V Block. Chronic heart block can rarely be traced to diphtheria. Jones and White,⁴ in a study of 100 consecutive cases who had had severe diphtheria 5 to 8 years previously, found none with evidence of heart disease. Butler and Levine⁵ have reported 20 cases of heart block of unknown origin, 10 of which previously had had diphtheria; of the 10 cases with a history of diphtheria only 3 were under 50 years. It appeared to them that the development of heart block in later years may be a sequel to diphtheria in childhood.

In the following 4 cases of complete A-V block the only known etiologic factor was previous diphtheritic infection. Each had proven complete A-V block or syncope attacks at an age when coronary heart disease was unlikely. None had any evidence of congenital heart disease although this possibility could not be ruled out definitely. Three had had diphtheria early in life and were aged 24, 27, and 28 years, respectively, when first examined by us; each had slight cardiac enlargement but none had attacks of dizziness or syncope and their response to exercise was normal. The fourth, aged 60, had had diphtheria 25 years previously and from that time suffered frequent attacks of dizziness and syncope; the heart was not enlarged but exercise tolerance was moderately decreased.

Repeated electrocardiograms in each instance showed complete A-V block.

Three of the patients are alive and fairly well at an average of 14 years and 8 months after the discovery of the conduction defect. The fourth case, aged 60, died of "heart disease" 4 years after the proof of the block and 29 years after the probable onset.

The response to exercise and atropin in 1 patient of this group is of some interest. While at rest the auricular rate was 60 and the ventricular 43. After exercise the auricular rate rose to 143 and the ventricular rate to 107, the block remaining complete. A similar but less marked rise was observed after gr. $\frac{1}{30}$ atropin sulphate was given subcutaneously. The explanation was not entirely clear; presumably the factor responsible for the block had not destroyed the vagal influence on the idioventricular pacemaker.

Miscellaneous. There remain for consideration 4 cases with coronary and rheumatic heart disease, 2 with coronary and probable luetic heart disease, 1 with coronary and probable luetic or rheumatic heart disease, and 2 with completely uncertain etiology. For obvious reasons it is not worth while to consider these cases in detail.

There were 5 males and 4 females with an average age of 45 years. All had some degree of cardiac enlargement and all had symptoms of cardiac weakness. All save 2 had cardiocerébral attacks. Seven have died of cardiovascular disease on an average of 2 years and 4 months after discovery of the block, while 1 remains alive but in poor health 6 years and 8 months after the discovery of the block. The remaining case was alive and well when last heard from in May, 1927.

Discussion. Only 72 patients with complete *A-V* dissociation have been seen at this hospital during a period of 19 years in which time electrocardiograms have been taken on about 14,000 patients.

While coronary heart disease was found to be the chief cause of the block it is worth noting that in about one-fourth of the cases other factors were responsible, namely, congenital, rheumatic, luetic, or diphtheritic heart disease. Some additional causes, not illustrated in this series of cases, are certain acute infections, poisoning, especially by drugs of the digitalis series, tumor, and trauma.

The sex and age incidence reflect that of the disease causing the block. Thus, patients with coronary heart disease were in the later decades of life and males outnumbered females more than 2 to 1, whereas patients with congenital heart disease were in the early decades of life and females outnumbered the males.

The cardiac symptomatology may be divided into two categories, that associated with the underlying heart disease and that associated with the block itself. The latter deserves especial mention.

Morgagni,⁶ in 1761, adequately described the syndrome of fainting associated with slow pulse rate but his report went unrecognized for many years. Adams,⁷ in 1827, and Stokes,⁸ in 1846, described more fully additional cases, and Huchard,⁹ in 1899, proposed the name of "disease of Adams or of Stokes-Adams" for this syndrome of bradycardia and syncope. Lewis¹⁰ has pointed out that "however probable it is that heart disease and high-grade block were present in these cases, the exact nature of the fits is unknown." Regardless of its unsuitability, it appears that the term Adams-Stokes or Morgagni-Adams-Stokes attacks will persist, although a decidedly better classification could be outlined under the heading of cardiocerebral attacks. Three grades of disability are commonly recognized: 1, the vertiginous attacks ("formes frustes" of Huchard) in which consciousness is not lost: 2, syncopal attacks and 3, convulsive seizures. These symptoms are caused by cerebral anemia and occur when the ventricles beat too slowly or stop entirely.

About two-thirds of the patients in our own series complained of attacks of dizziness, syncope, or convulsions.

The average ventricular rate in this series of cases was 40 a minute, which is faster than is commonly thought for complete $A-V$ block. In 17 instances (23.6%) there was a greater than 5% variation in the time between the slowest and fastest ventricular rates. This arrhythmia when coupled with the more rapid ventricular rates adds difficulty to the clinical recognition of complete $A-V$ block.

Partial or complete bundle-branch block was an associated finding in 42 instances (58.3%). This association is expected in view of the small area occupied by the bundle of His and its chief branches.

The slow regular heart rate observed in these cases rarely requires treatment; in fact it may occasionally be an asset. It is when the ventricles beat very slowly or become irregular that symptoms supervene and efforts are made to increase the rate or abolish the irregularity. Adrenalin and ephedrin were the only drugs found valuable in our series.

The prognosis of the patients in this series reflected that of the causal factor responsible for the block. For those with coronary heart disease it was poor, although exceptionally a patient lived more than 10 years.* The prognosis was very good in those with congenital or diphtheritic heart disease while in those with luetic or rheumatic disease it was fair. The outstanding impression gained after reviewing these cases is the necessity for distinguishing clearly between the conduction defect and the heart disease with which it may be associated. When complete $A-V$ block is present in an otherwise normal heart the bearer may enjoy a normal active life. Its chief significance does not lie in itself for it is rarely the immediate cause of death, but in the fact that it usually declares the presence of a serious and widespread affection of the ventricular musculature; as such it is an important sign and alters unfavorably the prognosis.

A Curious Form of Auricular Arrhythmia Frequently Observed in Complete Heart Block. Erlanger and Blackman¹¹ in their studies on experimental complete heart block in the dog, observed, occasionally, a peculiar periodicity of the auricles apparently dependent upon ventricular activity. They noted that the first auricular cycle following a ventricular contraction was long but that the successive auricular cycles shortened until the ventricle again contracted. Sometimes this auricular retardation was so marked that only a single contraction occurred in each ventricular cycle. This phe-

* Two exceptional instances of heart block in very elderly patients are worth mentioning. H. L., a widow, with coronary heart disease, had complete heart block for 4 years before she died of intestinal obstruction at the age of 86. F. M., a male clerk, aged 80, has had partial or complete heart block over 12 years; at present he is slightly active and fairly well.

nomenon was observed only during complete repose in dogs with heart block of comparatively long duration. They believed variations in vagal tonus, which increased with each arterial pulse and decreased during the interval between pulses, were responsible.

Hecht,¹² in 1913, published electrocardiograms showing high grade block found in a child of 5 years. He noted that the auricular cycles which contained a ventricular contraction were shorter than the rest. No explanation was offered and he did not comment on the electrocardiogram which showed that the arrhythmia was abolished when the child was given atropin. Wilson and Robinson¹³ observed the same kind of auricular arrhythmia in a case of complete heart block in an adult. They observed the disappearance of this arrhythmia when the auricular rate was increased after exercise or atropin. Two possible explanations were offered; first, that it was dependent on vagus activity, and second, that it was the mechanical effect of ventricular systole on the auricular pacemaker.

We have observed this type of auricular arrhythmia (Fig. 1) in 20 of the 72 cases in this series. It was not necessarily a constant phenomenon; that is, it would be exhibited on one occasion but not on another under circumstances apparently similar. It was observed to disappear with the increase in auricular rate after atropin or other cause. When the ventricular period contained two or more auricular cycles it was seen that the first auricular cycle following the ventricular contraction was long and the successive cycles shorter.

In considering the possible mechanisms of this arrhythmia one of the first points to decide is whether the auricular cycle containing the ventricular contraction is shortened or whether the succeeding auricular cycle is lengthened. This question is apparently answered in those examples where the ventricular period contains two or more auricular cycles. It is clearly to be seen that it is the first auricular cycle following the ventricular contraction which differs notably from the rest; the remaining cycles are shorter and do not differ greatly in length whether or not they contain a ventricular contraction. This leaves little to be said in favor of the view that the auricular cycle containing the ventricular contraction is shortened by the mechanical effect of ventricular systole on the auricular pacemaker; were this true all subsequent auricular cycles should be similar in length. We are inclined to the opinion that under certain conditions ventricular systole increases vagal tone possibly through the carotid sinus mechanism or directly through the arterial impulse in the sino-auricular artery or otherwise. We believe this is the usual mechanism, although very exceptionally electrocardiograms have been observed, apart from those instances of obvious ventriculo-auricular retrograde conduction, in which certain ventriculo-auricular sequences suggested that ventricular systole hastened auricular contraction. We have not observed this form

of ventriculo-auricular relationship in any of the electrocardiograms in this series.

Summary and Conclusions. 1. Seventy-two cases of complete A-V dissociation are briefly analyzed. Coronary heart disease was associated in 47 of the patients, congenital heart disease in 4, possible congenital heart disease in 2, rheumatic heart disease in 3, cardiovascular lues in 3, and possible chronic diphtheritic heart disease in 4, while the remaining 9 cases were of mixed or entirely uncertain etiology. Two-thirds of the cases (48) were male and one-third (24) were female; it was particularly in the coronary disease and syphilitic groups that the males predominated (36 to 11 in the former and 3 to 0 in the latter).

2. The heart disease responsible for the block in these cases affects the clinical course, treatment and prognosis far more than does the block itself.

3. Attacks of dizziness, syncope, or convulsions, symptoms related to the block itself, were present in 44 of the 72 cases; in 4 instances they were the probable cause of death. Adrenalin and ephedrin were the only drugs found valuable in the treatment of these attacks.

4. The prognosis of those patients in this series with coronary heart disease was generally very poor although there were striking exceptions; for those with congenital or old diphtheritic heart disease it was good, while for those with luetic or rheumatic disease it was fair.

5. A form of auricular arrhythmia frequently observed in these cases is discussed.

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OBSERVATIONS ON SOME OF THE PHYSIOLOGIC EFFECTS OF
THE CORRECTION OF FAULTY POSTURE.

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THE correction of faulty posture involving the thoracic and lumbar spinal curves has been considered a mechanical advantage to the body and a valuable adjunct to the treatment of many visceral disorders.¹ This belief is supported by considerable clinical evidence. Faulty posture is certainly capable of producing various symptom complexes of referred pain which may be completely relieved by training the patient to assume a proper stance. If, however, the routine correction of postural defects is to be granted a position in the generally accepted treatment of disorders which are not essentially orthopedic, more precise information should be available concerning the influence of posture on the body function. An attempt has, therefore, been made to estimate some of the physiologic effects of changing from a kypho-lordotic posture to one regarded as optimum by orthopedic standards. The present study involves an analysis of the immediate results so observed. It is believed that these observations help to evaluate the therapeutic benefit to be expected from the orthopedic correction of postural defects.

Methods. A group of subjects was studied, which included 18 healthy adults of both sexes with B, C, and D posture according to the Harvard standards. Ten subjects were workers in the Occupational Therapy Clinic of the Graduate Hospital and symptom-free; 8 were patients of the Orthopedic Clinic who had symptoms referable to faulty mechanics. All had been trained in the ability to correct their postural defects.

All observations reported on each patient were obtained on the same day to insure comparable results, although preliminary periods of observation were usually made. The following studies were carried out with the subject standing first in the corrected, then in the faulty posture. 1. Orthodiagrams with special attention to the thoracic and cardiac measurements and the maximum diaphragmatic excursion. (Difference of less than 0.5 cm. were regarded as within the limit of experimental error. Diaphragmatic measurements were made from the highest point of the dome.) 2. Estimations of vital capacity obtained with a standard spirometer (the figures reported are the averages of the maximum values). 3. Electrocardiograms. 4. Estimations of oxygen consumption and graphic records of the respiration including measurements of tidal air and minute volume, obtained with a standard spirometer for metabolism determinations. 5. Repeated determinations of blood pressure and pulse rate over 10-minute intervals with preceding and intervening 10-minute intervals during which the subject was recumbent. On the basis of these readings a rating was obtained for circulatory efficiency in each of the two postures according to the method of Turner.²

Results. The changes observed on correcting a faulty posture are outlined in Table 1. It will be noted that there was a marked individual variation in the reaction of the different subjects and that the results bear no apparent relationship to their postural classification, whether B, C or D. These variations appeared to depend upon such factors as physical type, the extent of the physiologic handicap produced by the postural defect and the amount of physical strain incurred by correcting it. Thus the first conclusion which can be drawn is the fact that the therapeutic value of correcting a postural defect can seldom be estimated beforehand and that the amount of benefit acquired is not always directly proportional to the degree of the subject's "slump."

Transverse Diameter of the Chest. The measurements of the transverse diameter of the chest were made in the position of normal expiratory relaxation. Of the 18 subjects, 9 showed no significant change on correcting the faulty posture, 7 showed a slight increase of 0.5 to 1.8 cm., while 2 showed a decrease of approximately the same value. Apparently the chest becomes somewhat wider in the presence of either extreme correction or extreme slump. In the correct posture, straightening of the spine causes an increase in the rib angles with outward flaring of the chest. In the excessively slumped posture, the lower part of the chest tends to widen due to upward compression of the abdominal viscera.

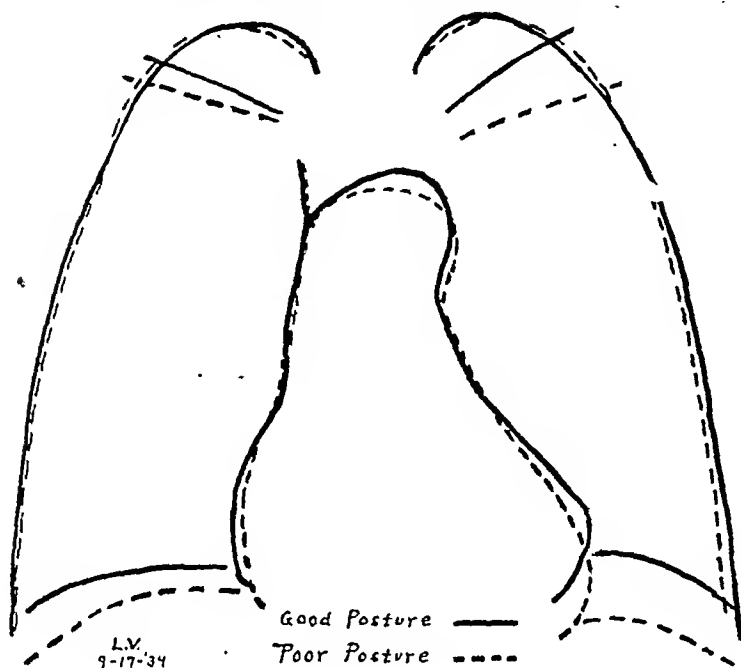
Position of the Diaphragm. Orthodiagraphic illustrations of the chest in the corrected and slumped postures always show the diaphragm higher in the former.¹ In our experience this relationship has not been constant. In 7 cases the diaphragm was higher in the corrected than in the faulty posture (*i. e.*, with respect to the top of the chest); in 4 there was no significant difference between the two positions; in 7 the diaphragm was higher in the slumped posture (Fig. 1). This difference may be explained as follows: On assuming a corrected posture, the abdominal wall is drawn in and the diaphragm pushed upward. At the same time the thoracic spine straightens and the chest elongates on its vertical axis. The diaphragm, therefore, is raised with relation to the pelvis but not necessarily with relation to the top of the chest. This fact is of considerable interest. If coincident elongation of the chest does not occur, the elevation of the diaphragm will diminish the chest volume and may become a handicap to pulmonary function. Thus in the presence of irretractable kyphosis it may be a disadvantage to cause elevation of the diaphragm if an adequate increase in thoracic volume cannot be obtained by straightening of the thoracic as well as the lumbar spine. This is not necessarily a handicap in cases of emphysema where the lung is already overexpanded as it has been shown that elevation of the diaphragm permits increase in the vital capacity.³

Position of the Heart. Change from a faulty to a corrected posture is said to involve an increase in the transverse diameter of the

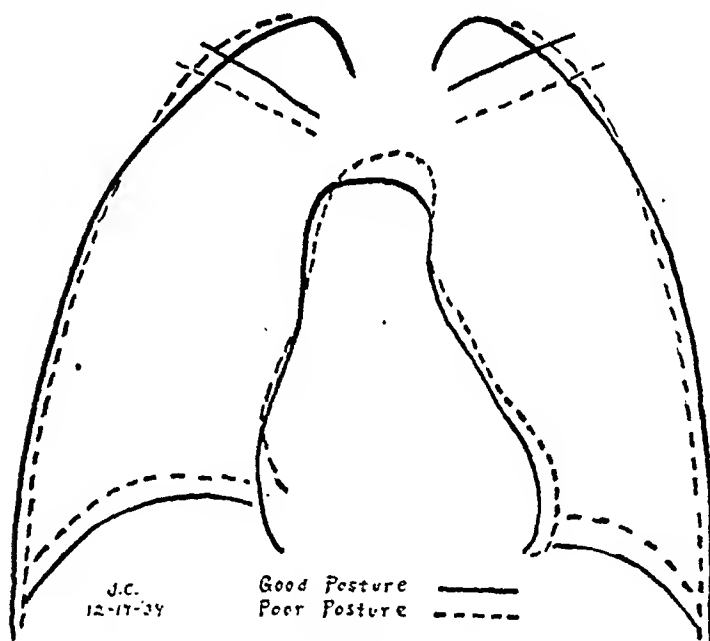
TABLE 1.—THE EFFECTS OF CORRECTION OF POSTURAL DEFECT.

Subject Posture class	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	Average	
																			+	-
Transverse diameter of chest	0	0	0	-1.3	+0.5	0	0	+0.6	0	+1.7	0	+1.8	0	-0.5	+1.0	+0.5	+1.0	0	7	2
Height of diaphragm	1.5	0.7	0	+0.6	0	1.5	0	0	+1.6	+0.8	+1.9	+0.7	1.0	+2.5	-	2.1	0.8	+1.2	7	4
Transverse diameter of heart	0.6	1.5	1.1	0	0.7	0.5	0	0	0	+1.3	0	+0.7	1.7	+0.5	1.0	0	0.6	0	3	7
E. C. G. axis shift to-ward left	-	-	0	0	+	-	0	+	0	0	+	+	-	+	-	-	0	0	5	4
Excursion of dia-phragm	+1.5	+1.8	+1.0	-1.2	-3.4	-0.5	-1.5	0	+1.6	-1.8	+1.5	+0.8	-1.0	+2.0	+1.0	+1.6	-1.4	-0.9	7	4
Vital capacity	0	0	+100	+510	0	+110	+0.9	+116	0	+494	+260	+575	+257	0	0	+240	-360	0	10	7
Respiratory rate	+3	-4	-8	+2	0	0	-10	-2	0	-5	0	-1	-11	+3	-3	+3	-1	-2	10	3
Tidal air	-55	+825	+545	+232	+48	0	+333	+106	.	+625	+341	+171	+668	-254	+166	+122	+510	+26	14	1
Respiratory minute volume	+320	5480	3030	4120	1010	480	470	1190	0	4270	1520	6030	980	2500	4880	8720	+233	0	13	1
Oxygen consumption	0	-103	+17	0	-30	+67	+40	-76	-6	0	+	-46	+36	+	0	-57	+233	0	16	5
Circulatory efficiency	0	+14	0	+8	+2	+1	-1	+	+	+9	+	0	+2	-3	-3	+15	+1	+3	11	3

0 = no change upon shifting from a faulty to a correct posture; + = increase; - = decrease.



A



B

FIG. 1.—Orthodiagram: broken line indicates poor posture; continuous line, good posture. A, shows Subject 14 in whom the diaphragm is higher with respect to the top of the chest and the heart more transverse in the corrected posture. B, shows Subject 15 in whom the diaphragm is lower with respect to the top of the chest and the heart is less transverse in the corrected posture.

heart due to elevation of the diaphragm.¹ In the present study it was found that just as the height of the diaphragm with respect to the top of the chest is not always increased by the correction of a postural defect, neither does the heart always become more transversely placed. In only 3 cases was the cardiac transverse diameter significantly increased; in 7 it remained unchanged while in 8 it was actually diminished. This observation was confirmed by the electrocardiogram, which in the corrected posture showed the electrical axis of the heart to be shifted toward the left in 5 cases and toward the right in 7, while in 4 it remained unchanged. In 10 cases the axis shift corresponded with the observed change in the cardiac measurement; in only 1 case was it at variance. In the remaining cases either the electrical axis of the heart or the measured transverse diameter was unchanged.

Although the transverse diameter of the cardiac silhouette tends to increase when the diaphragm is elevated by the corrected position, it may actually decrease under the following circumstances: 1, when the heart is sufficiently elevated by its attachments to the cervical fascia and, therefore, becomes more dependent; 2, when the heart is elevated by the rise of the diaphragm rather than by upward traction of its mediastinal attachments, but tends to rotate in a horizontal rather than a vertical direction. The degree to which these phenomena occur varies between individuals and with the physical type of chest and its contents and could be observed under the fluoroscope. The occasional lack of correspondence between the measured cardiac silhouette and the angle of the electrocardiographic axis depended upon the fact that the two are similarly altered by vertical rotation of the heart but not necessarily by horizontal rotation or lateral displacement.

Diaphragmatic Excursion. The maximum diaphragmatic excursion between forced inspiration and expiration occurred in the corrected posture in 7 cases and in the slumped posture in 7. In 4 cases the change was not considered significant. This difference in some subjects was apparently due to the upward compression of the diaphragm in the correct posture being predominantly advantageous by favoring a more complete expiration; in others it was predominantly a disadvantage by impeding inspiration. As will be shown later, the extent of the maximum diaphragmatic excursion is not directly proportional to either the vital capacity or the average depth of respiration, both of which are influenced by thoracic excursion as well. It is clear from these observations that the posture which is most favorable to diaphragmatic function may, for certain individuals, be one which is not perfect by orthopedic standards.

Vital Capacity. In 10 cases the vital capacity was increased on assuming the corrected posture (average when increased, 307 cc.), in 7 cases it was not significantly altered and in only 1 case was it decreased. Although there is no doubt as to the improvement of the

vital capacity in the corrected posture, it was noted that when erect many of the subjects stooped somewhat to complete expiration, and when slumped they became momentarily more erect during the preliminary inspiration. From this it appears that although an increased vital capacity is favored by the corrected posture, too rigid correction may tend to diminish it and a certain flexibility is requisite for optimum results.

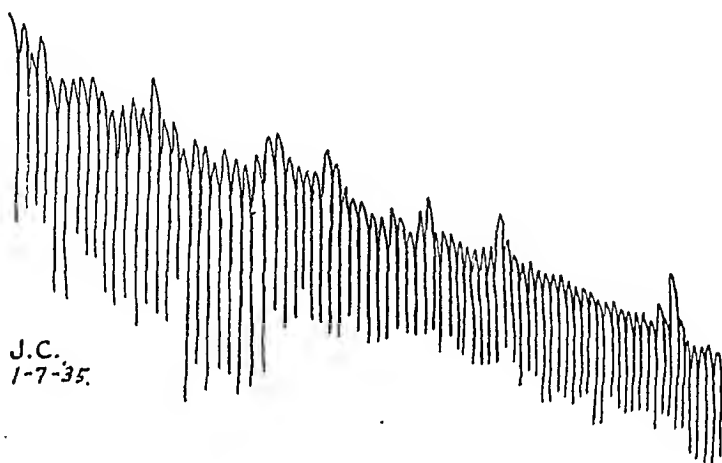
The vital capacity is intimately related to cardiac and respiratory function. It is decreased in the presence of various disorders of the heart and lungs. In cases of this type an optimum stance is often assumed instinctively. In such cases it is probably a mistake further to correct a minor postural error, since to do this may produce a physiologic handicap. Other patients, however, because of fatigue or the therapeutic restriction of exercise, become increasingly relaxed and stooped. Under these circumstances it is justifiable to expect that an increase in the vital capacity attained by orthopedic training may afford a marked degree of symptomatic benefit. Care should be taken, however, that the posture so assumed is actually optimum for the individual and that the circulation is not further embarrassed by too rapid correction.

Electrocardiogram. No significant changes in the electrocardiogram were found which were attributable to posture, except for a shift in the electrical axis of the heart described above. This shift was indicated by variations in amplitude of the *R* and *S* waves in Leads I and III. Rarely the amplitude of the *T* waves in Lead III was similarly influenced but to a very slight degree.

Incidentally records taken in the corrected posture of many subjects showed a much higher degree of muscle tremor than those taken in the slumped posture. This was a manifestation of greater physical strain associated with the unaccustomed posture and indicates the fatiguing effect of maintaining it for long periods of time.

Oxygen Consumption. The measurements of oxygen consumption are necessarily subject to a considerable degree of experimental error and can be considered significant only in the direction and not in the quantity of change. Of 16 subjects in whom estimates could be made, 5 showed no difference in the two positions, 6 showed the highest value in the good posture and 5 in the poor posture. The rate of oxygen consumption under the circumstances is influenced by many factors including the fatigue of standing, the relative degree of strain involved by the corrected posture, the amount of respiratory effort and the amount of oxygen available to the tissues. Although these results are at best only suggestive, the impression was gained that oxygen normally tends to be utilized somewhat less rapidly in the corrected posture. In the present study the effect of strain in subjects whose habitual stance was slumped was very apparent, especially in the electrocardiogram. If this strain were eliminated by adaptation to the corrected posture, it is likely that the higher oxygen consumption values would be definitely reduced.

Respiration. The effects on respiration of the corrected as compared with the slumped posture included: 1, Slower rate; 2, increased depth of respiration (tidal air) and 3, increased pulmonary ventilation (respiratory minute volume). The type of graphic record obtained is illustrated in Figure 2. There were a few exceptions but they were not considered significant. The characteristic effects occurred not only in subjects who were accustomed to the correct posture, but also in subjects to whom it was still a physical strain.



Good posture:		Poor posture:	
Resp. rate	13 /min.		21 /min.
Tidal air	1,012 cc.		467 cc.
Min. vol.	12,850 cc.		9,820 cc.
O ₂ consump.	263 cc./min.		246 cc./min.

FIG. 2.—Respiration and oxygen consumption in the correct and incorrect postures—Subject 2.

Three artificial influences must be taken into account in considering the graphic respiratory records obtained: 1, The subject breathed through a spirometer (the effect of which was minimized by a "motor blower"); 2, breathed through his mouth, and 3, breathed pure oxygen. Although the records do not represent entirely normal conditions, they are, however, at least comparable and indicate the direction and proportion of change under physiologic circumstances.

In the corrected posture, respiration is apparently facilitated by an increased latitude for diaphragmatic and thoracic excursion (vital capacity) and tend to be deeper and, therefore, slower. Less clear, however, is the reason for the increased respiratory minute volume. It bore no evident relationship either to oxygen consumption or to circulatory efficiency. To what extent it is an artifact due to the type of graphic recording or how much it was influenced by physical strain is uncertain. It seems probable, however, that it is also present, at least to some degree, under normal physiologic conditions.

Cardiovascular Efficiency. The criteria adopted by Turner for the appraisal of cardiovascular efficiency² were applied to the estimations of blood pressure and pulse rate taken over 10-minute intervals in the two postures. Eleven subjects had a better rating in the corrected posture, 4 in the slumped posture and 3 showed no significant change. There appeared a tendency in the slumped posture for the pulse rate to increase, for the blood pressure to fall and for both to manifest less stability than in the corrected posture (Fig. 3). In the majority of subjects these differences were not striking and might be overlooked unless compared by circulatory efficiency standards. In Subjects 2 and 16, however, examples were obtained of an extremely unfavorable effect of faulty posture on the circulation. In both cases the blood pressure fell rapidly from its initial level, the pulse rate became markedly accelerated and the patient

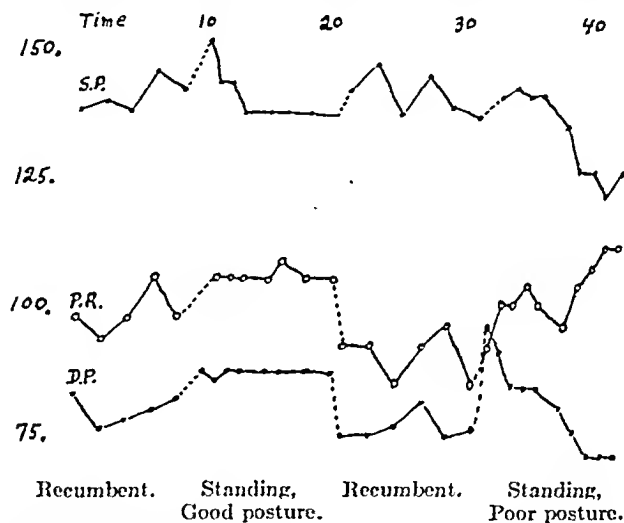


FIG. 3.—Blood pressure and pulse rate in the correct and incorrect postures—Subject 15.

complained of faintness. In the corrected posture these events did not occur. These individuals evidently had a tendency toward postural hypostatic congestion (a condition which is more common than is usually realized). In such cases, hypostatic congestion and the resultant cerebral anemia, may be prevented by the action of the abdominal muscular tone in compressing the splanchnic blood reservoir. This effect, together with the increase in vital capacity, make the correct posture a distinct advantage to cardiovascular function in the majority of cases, while in a few cases its influence may be spectacular.

Discussion. It is again pointed out that these observations concern only the immediate results of change in posture; to what extent the effects are permanent or may be modified by the adaptation of the subject to an improved stance can be determined only after a

lapse of sufficient time and under strictly comparable experimental conditions. There is also an unavoidable element of experimental error associated with the methods employed. But even with due allowance for these factors, we believe that the following opinion is substantiated: Correction of faulty posture is generally a significant advantage to circulatory and respiratory function, and in some cases may have important therapeutic value. All individuals, however, are not equally or similarly benefited. The differences in effect do not appear to depend entirely upon the degree of the defect, but rather upon the degree to which the patient is handicapped by the defect. Full correction of posture is sometimes unfavorable to maximum physiologic efficiency. Too rapid change from a poor to a corrected posture is also likely to be fatiguing and obscure the benefit otherwise derived. Rarely it is possible that an orthopedically faulty posture may be a compensatory adaptation of the body to other abnormalities and should not be changed.

Summary and Conclusions: 1. Eighteen healthy subjects with postural defects of the kypholordotic type were studied with respect to the immediate physiologic changes produced by correction of posture.

2. Corrected posture did not always produce an elevation of the diaphragm with respect to the top of the chest nor did the heart always become more transversely placed. The cause and significance of these facts are discussed.

3. The vital capacity was increased by assuming a corrected posture but it was noted that flexibility of posture was essential in obtaining optimum results.

4. The respirations in the corrected posture became slower and deeper and the respiratory minute volume was increased.

5. The oxygen consumption was not altered in a consistent manner but there was suggestive evidence that under normal conditions it is lower in the corrected than in the faulty posture.

6. Blood pressure and pulse-rate changes on standing indicated in the majority of subjects a better degree of circulatory efficiency in the corrected posture. In 2 cases the corrected posture was able to prevent a postural hypostatic congestion.

7. It was concluded that the correction of postural defects has a significantly beneficial effect on circulatory and respiratory function in the majority of cases. Its value varies considerably between individuals for reasons which are not always evident. In some cases, its effect may be spectacular. Full correction may occasionally be a physiologic handicap. For each individual there is an optimum posture, the attainment of which produces the maximum therapeutic benefit.

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INTRA-ABDOMINAL TORSION OF THE APPENDICES EPIPLOICÆ.

WITH REPORT OF TWO CASES AND REVIEW OF THE LITERATURE.

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THE appendices epiploicæ occur along the entire colon from the cecum to the rectum, being most numerous in the transverse and pelvic colon. They appear in two rows, originating in relation to the anterior muscular band and the postero-internal band; rarely a third row is observed, and occasionally only one row is present. They have been described as pouches or processes of peritoneum, which contain a variable amount of fat, usually considerable in obese persons (Hunt). The blood supply for each consists of one artery and one vein; arising from the superior and inferior mesenteric arteries, and emptying into the superior and inferior mesenteric veins.

The physiologic function of the appendices epiploicæ is not clearly understood. Robinson believes that they are concerned with the movement of fluids in the large bowel. The anatomic confinement of the appendices epiploicæ to the colon where fluids are reabsorbed makes this theory quite probable. He pointed out the dissimilarity between the structure of these processes and the great omentum as a refutation of the protective theory which is held by some authors. The fact that these structures have been found adherent to other inflamed abdominal viscera is not adequate proof of their protective nature. Patterson has suggested that they may act simply as bumpers for the large intestine, fending it from the parietes and other viscera, thus facilitating peristalsis.

Their pathologic changes are chiefly due to mechanical interference with the blood supply or inflammation. Torsion, either within the abdomen or within a hernial sac, is the most frequent cause of disturbed blood supply. Simple incarceration of an appendix epiploica within a hernial sac may be sufficient to cause gangrene. Inflammatory reactions in the form of fat necrosis, subperitoneal hemorrhages and gangrene usually follow a disturbance of blood supply. As a result of sudden torsion the appendix epiploica may become detached, forming a free foreign body within the peritoneal cavity, or it may become calcified remaining attached or becoming detached. Bacterial invasion leading to pure inflammatory changes may occur from an associated diverticulitis. Intestinal obstruction has been produced by adherent bands formed following disease of the appendices epiploicæ. Local peritoneal abscesses and general

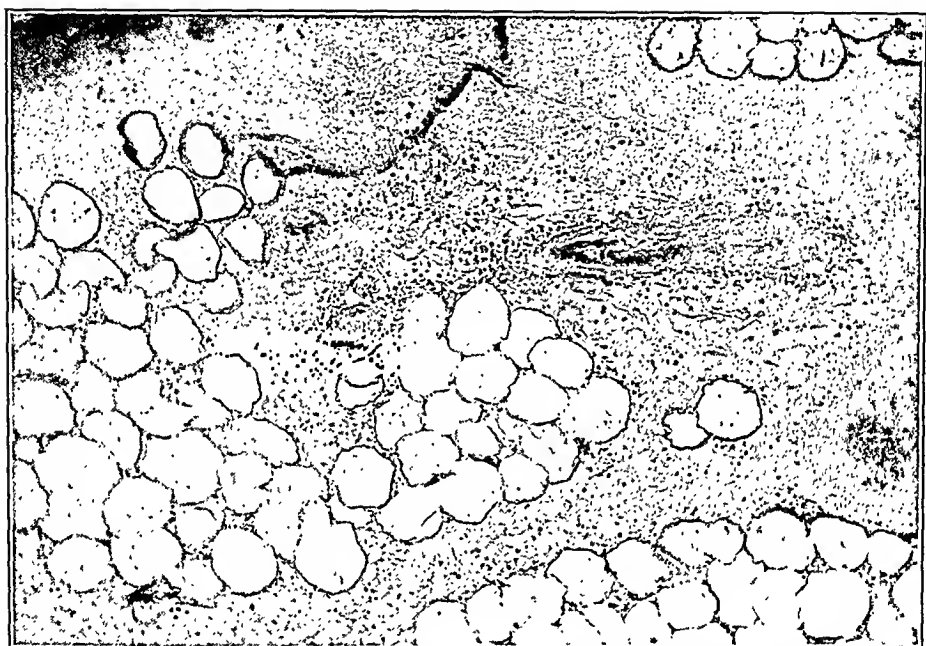


FIG. 1.—Appendix epiploica showing partial thrombosis of central vessel with perivascular leukocytic infiltration. Note the hemorrhage throughout the tissue.

peritonitis have been attributed to disease of the appendices epiploicæ.

Of the pathologic changes occurring in the appendices epiploicæ, intraabdominal torsion and inflammation are the most common. All cases reported as torsion within a hernial sac and as loose foreign bodies within the peritoneal cavity have been omitted in this paper.

Review of the Cases Reported in the Literature. The first 16 cases of intraabdominal torsion of the appendices epiploicæ were abstracted and reported by Hunt in 1919. Since no additional cases were found these cases were not included in our tabulation but have been referred to by number in the bibliography, the case number and bibliography number corresponding.

Report of Two Cases. **CASE 43 (24014).** A female, aged 42, was admitted to this hospital, service of Dr. W. Wayne Babcock. Three days before, she was seized with sharp pain in the lower left abdomen, following an attack of coughing. The pain became dull, constant and was made worse by motion. Vomiting occurred for the first and only time after eating dinner the night before admission. The bowels were moved for the first time, since the onset of pain, the night before admission by an enema, this increasing the pain. There were no previous attacks. The appendix vermiformis had been removed 22 years ago. Ten years ago she had an operation for a ruptured ectopic pregnancy. The temperature was 99° F., the pulse rate 90. The abdomen was somewhat obese but not rigid or distended. A deep-lying, tender, nodular, mass the size of a bean was palpated about mid-way between the left anterior superior spine and the umbilicus. The leukocyte count was 11,700 with 75% neutrophils. A pre-operative diagnosis of torsion of an appendix epiploica was made by Dr. Babcock.

Under spinal anesthesia the abdomen was opened through a 10 cm. left transverse muscle-splitting incision. Arising from the sigmoid an appendix epiploica measuring 18 by 30 by 10 mm., purple-red in color, was found and removed by ligation of the base. There was no torsion of the pedicle. The surrounding peritoneum was injected and covered with plastic exudate. Adjacent non-inflamed diverticula of the sigmoid were observed. Pathologic report was acute inflammation, thrombosis and hemorrhage of an appendix epiploica (Fig. 1).

The patient was discharged in 13 days. Until the present, 14 months later, there have been no abdominal symptoms.

CASE 44. A male, aged 27, was admitted to the service of Dr. Babcock. He complained of pain, increased by motion, in the left lower abdomen, of gradual increasing severity and of 24 hours' duration. There was no nausea or vomiting. The bowels were moved by an enema at the onset of the pain and moved normally the day of admission. Four months previous he was in the hospital complaining of generalized abdominal pain associated with nausea and vomiting. The diagnosis of subsiding appendicitis or gastroenteritis was made, and he was discharged in a few days. Otherwise there was no history of previous abdominal symptoms. The patient was well developed. There was tenderness on slight pressure in the lower left quadrant, no masses or abdominal rigidity. Rectal examination produced pain and tenderness above and to the left of the prostate gland. The leukocyte count was 9800 with 70% neutrophils. A pre-operative diagnosis of diverticulitis was made.

The abdomen was opened through a 10 cm. transverse muscle-splitting incision mid-way between the left anterior superior spine and the umbilicus.

TABLE 1.—ABSTRACTS OF CASES OF INTRA-ABDOMINAL TORSION SINCE 1919.

Case No.	Sex and age.	Symptoms.				Pre-operative diagnosis.	Origin of diseased appendix epiploica.	Comments.
		Pain.	Duration.		Miscellaneous.			
			Location.	Acute.				
17	F. 35	R. L. Q.	2 days	10 mos.	T. and R. right rectus, obese	Acute appendicitis	Ascending colon	Incidental appendectomy.
18	F. 51	L. L. Q.	3 days	2 yrs.	T. and R. left rectus, mass	Twisted ovarian cystoma	Sigmoid	Turbid peritoneal fluid, plastic exudate.
19	M. 60	L. L. Q.	4 days	T. L. L. Q., indefinite mass	Acute appendicitis, left	Lower descending colon	Edema peritoneum; gangrene of appendix epiploica.
20	M.	R. L. Q.	N. and V. 2 attacks in 4 weeks	Acute appendicitis	Cecum	Incidental appendectomy.
21	F. 14	L. L. Q.	12 days	Symptoms of peritonitis	Degenerated myomata	Sigmoid	Appendectomy, hysterectomy, bilateral salpingo-oophorectomy, peritonitis.
22*	F. 45	Epigastric	4 hrs.	Symptoms due to acute pancreatitis, obese	Peritonitis	Transverse colon	Torsion of appendix epiploica was incidental autopsy finding.
23	M. 45	R. L. Q.	?	Tenderness R. L. Q.	Acute appendicitis	?	Twisted appendix epiploica around perforated appendix.
24	F. 39	R. pelvic L. L. Q.	2 days	15 yrs.	T. L. L. Q., tender swelling by vagina, obese	Torsion of ovarian cyst	Sigmoid	Appendectomy.
25	F. 39	R. L. Q.	8 days	Tenderness and rigidity. R. L. Q.	Subacute appendicitis	Ascending colon	Caution! Microscopic degenerated fibroma.
26	F. 35	R. L. Q.	2 days	T. above Poupart's lig. and rectal	Subacute appendicitis	Cecum	Appendectomy.
27	M. 53	R. hypochondrium	36 hrs.	Tenderness, obese	Acute appendicitis	Ascending colon	Appendectomy.
28	M. 43	R. L. Q.	5 days	Occasional nausea	Acute appendicitis ?	Sigmoid	Appendectomy. Serous peritoneal fluid.
29	M. 54	R. L. Q.	2 days	Tenderness and rigidity	?	Ascending colon	Kinked chr. appendicitis with twisted append. epip. adherent at kink.
30	F. 33	Lower abdomen	Long time	Unable to work on account of pain	?	?	Multilocular cysts of append. epip. containing clear fluid. Appendectomy.
31	F. 33	Lower abdomen	Chronic	Pain relieved by 2 hours in bed	Recurrent appendicitis	Sigmoid	

* See note on Table 2.

TABLE 2.—ABSTRACTS OF CASES OF INTRA-ABDOMINAL TORSION SINCE 1919.

Case No.	Sex and age.	Symptoms.				Pre-operative diagnosis.	Origin of diseased appendix epiploica.	Comments.
		Pain	Duration		Miscellaneous.			
			Location.	Acute.				
32	F. 50	Epigastric	3 wks.	Diarrhea, vomit, slight disten., tender and mass	?	Sigmoid	Facial erysipelas; postoperatively.
33	F. 51	L. L. Q.	5 yrs.	Increasing constipation, 5 yrs.; nausea and ocea. pain	?	Sigmoid	Appendectomy.
34	F. 38	L. L. Q.	4 yrs.	Pain followed appendectomy; 5 yrs. ago	?	Sigmoid	Descending colon distended.
35	M. 64	R. L. Q.	4 hrs.	Nausea and vomiting; tender	Acute appendicitis	Sigmoid	No torsion of pedicle. Thrombotic or embolic.
36	M. ?	L. L. Q.	2 days	Nausea; general tympanites; tenderness	Meckel diverticulum divert. sigmoid transposed append.	Sigmoid	
37	F. 52	R. L. Q.	12 hrs.	Tend. and sl. rigid., hacking cough, 3 days; obese	Acute appendicitis	Cecum	
38	M. 58	L. L. Q.	2 days	Vomit. intermitt., semi-obese; T. and R., tympanites	Intestinal obstruction	Sigmoid	Partial kink of sigmoid due to disease; app. epip.
39	F. 44	Postoperatively symptoms could not be related	Sigmoid	Torsion of app. epip.; incidental finding during hysterectomy.
40	F. 45	L. L. Q.	2 days	Obese, tender and rigidity; nausea	Torsion of ovarian cyst. diverticulitis	Sigmoid	Thin blood-stain peritoneal fluid.
41*	M.-mid. aged	Abdominal	3-4 days	Acute appendicitis, peritonitis ?	Sigmoid	Median Peritoneal abscess around gang. app. epip.
42	M.	L. L. Q.	?	?	Symptoms similar to those of left-sided appendicitis	?	Sigmoid	
* Death Epig.—Epigastrium		T—Tenderness N—Nausea	R—Rigidity V—Vomiting.	LLQ—Left lower quadrant	RLQ—Right lower quadrant			

A twisted blue-black appendix epiploica measuring 2.5 by 2.5 by 7 cm. was found and removed. Three adjacent yellow-gray appendices epiploicæ were resected. The vermiform appendix was not removed. Pathologic section showed hemorrhagic infarction of an appendix epiploica.

Convalescence was complicated by a pansinusitis, cervical adenitis, and muscular pains. Up to the present, 2½ years later, there has been no return of abdominal pain.

Discussion. To the 42 cases of intraabdominal torsion or infarction of the appendices epiploicæ reported in the literature we have added 2, bringing the total to 44 (23 males, 21 females). For 37 cases the average age was 44.3 years; the oldest 70, the youngest 20. Many authors state that obesity is a predisposing factor, however, it was directly mentioned or implied in only 15 of these cases.

There were no clinical symptoms referable to the diseased appendix epiploica in 5 cases; the condition being found incidentally at autopsy in 2 instances, and during a laparotomy for another condition in 3 cases. Of the remaining 39 cases, 32 presented acute abdominal symptoms necessitating operation, 8 of these cases also had a history of chronic symptoms, in the remaining cases the symptoms were entirely chronic in character. Abdominal pain is the only constant symptom; the character varies from sudden severe to chronic recurrent; in 3 cases it followed coughing or lifting; motion increased the pain in some cases. The pain was located in the lower abdomen in most cases, the left side was involved in 18, the right in 17, and in 2 cases it occurred in the epigastrium. Tenderness localized at the site of pain was recorded in 22 cases. Nausea was present in 10 cases and vomiting occurred in 8. In 7 cases an abdominal tumor was described.

The pathologic changes in all the cases were more or less similar, the appendix epiploica being somewhat enlarged; and blue, black, or purple in color. On section, thrombosis, hemorrhagic infarction, cellular infiltration, and fat necrosis were characteristic. The diseased appendix epiploica arose from the sigmoid in 26 cases, the cecum in 9, the ascending colon in 4, the transverse colon in 2 and the descending colon in 1. Torsion of the pedicle was described in all but 4 of the cases (Randall, Robertson, Ober and ours). Randall thought the lesion in the appendix epiploica was thrombotic or embolic in origin. In our case thrombosis of the central vessel was found on section, and we do not feel that the adjacent non-inflamed or adherent diverticula had any etiologic significance. Localized plastic peritonitis and peritoneal abscess were present in some cases. Intestinal obstruction was caused by the diseased appendix epiploica in 2 cases (Riedel and Hamilton).

A correct pre-operative diagnosis was not made in any of the cases reviewed. The diagnosis of appendicitis in some form was the most frequent error. Among the pre-operative diagnoses made were torsion of ovarian cyst, diverticulitis, tumor of the sigmoid,

tubo-ovarian disease, cholelithiasis, degenerated myomata, intestinal obstruction and paralysis and peritonitis.

There were 5 deaths in the cases reported; in 2 cases the condition was an incidental autopsy finding, 1 having died of cardiac failure and 1 of acute hemorrhagic pancreatitis. In 3, the disease of the appendix epiploica was directly responsible for death. The case reported by Riedel died 1 day after operation from intestinal obstruction caused by a twisted appendix epiploica arising from the cecum and adherent to the middle portion of a coil of mesentery of the small bowel. In the case of Ebner, death occurred on the seventh postoperative day of intestinal paralysis secondary to torsion of an appendix epiploica. Seelye reports a death occurring a few days after operation due to generalized peritonitis following drainage of an abscess caused by a twisted gangrenous appendix epiploica. This is adequate proof that torsion of the appendices epiploicæ is a serious condition which demands recognition and proper treatment.

Conclusions. 1. Intra-abdominal torsion and hemorrhagic infarction of the appendices epiploicæ are definite clinical entities. To the cases found in the literature, 2 are added.

2. The most characteristic clinical symptom was abdominal pain usually occurring over the site of the lesion. There may be associated localized tenderness. Nausea and vomiting were uncommon. A palpable tumor was present in 7 cases.

3. Intra-abdominal disease of the appendices epiploicæ resulted in complications causing death in 3 cases.

4. Pre-operative diagnosis is difficult. In any obscure case of abdominal pain which is not explained by operative findings, an exploration of the appendices epiploicæ should be considered.

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I wish to acknowledge my appreciation to Dr. Babcock for the use of these cases.

CEREBRAL LESIONS IN UNCOMPLICATED FATAL DIABETIC ACIDOSIS.*

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A DIABETIC ought not to die from uncomplicated coma. In the first place, barring an infection with sequential acidosis, that he is in coma is presumptive evidence of ignorance or neglect. In the second place, even though coma is present, adequate and early therapy should save the patient. Nevertheless, uncomplicated diabetic coma deaths continue to occur. In a total of 35 coma fatalities from 1923 to 1935 Joslin⁵ reported that 11 had no other complications. In our clinic from January 1, 1931 to July 1, 1935, 21 out of 52 coma deaths were uncomplicated. In the series here presented the criterion for coma is a plasma carbon dioxid combining power of 20 vol. % or less, though the difficulty resulting from an arbitrary figure is recognized. Almost all of our 21 cases were not hospitalized until hours after the beginning of the symptoms of oncoming coma.

The clinical picture of these patients in the terminal stages is strikingly similar, the outstanding features being the very low blood pressure, the rapid heart rate and usually a sharp rise in temperature. These features may be present when the patient is admitted but more often appear after the coma treatment has been begun. Not infrequently they are present when good response is obtained to treatment as measured chemically by a rising plasma CO₂. Lande⁶ has reported similar findings and found that recovery was rare in the presence of both cardiovascular failure and marked hyperpyrexia.

* Preliminary report given before the Philadelphia Neurological Society, December, 1934.

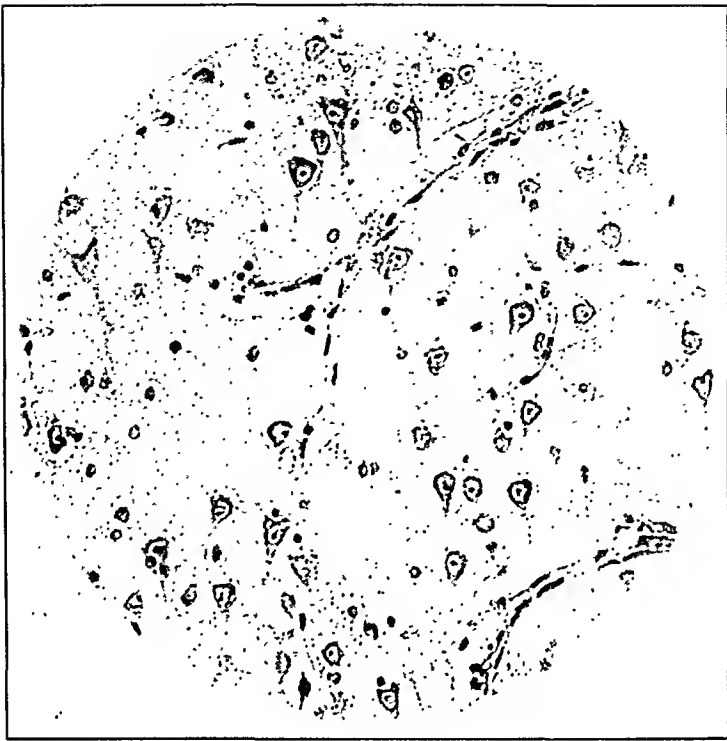


FIG. 1.—Case 3. Cortex showing perivascular and pericellular edema with degenerative changes in capillary endothelium. $\times 207$.

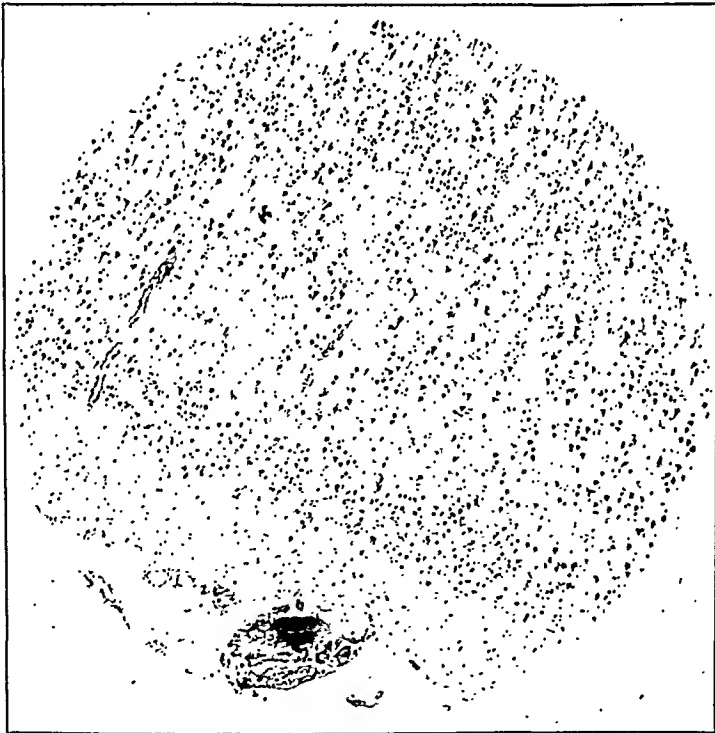


FIG. 2.—Case 7. Cortex showing cellular proliferation of the cortical vessels and focal areas of cell loss in third and fourth cortical layers (Brodmann). $\times 48$.



FIG. 3.—Case 6. Putamen and globus pallidus showing perivascular edema with fibroblasts and macrophages in the dilated perivascular spaces. Vessels show cellular proliferation. $\times 69$.

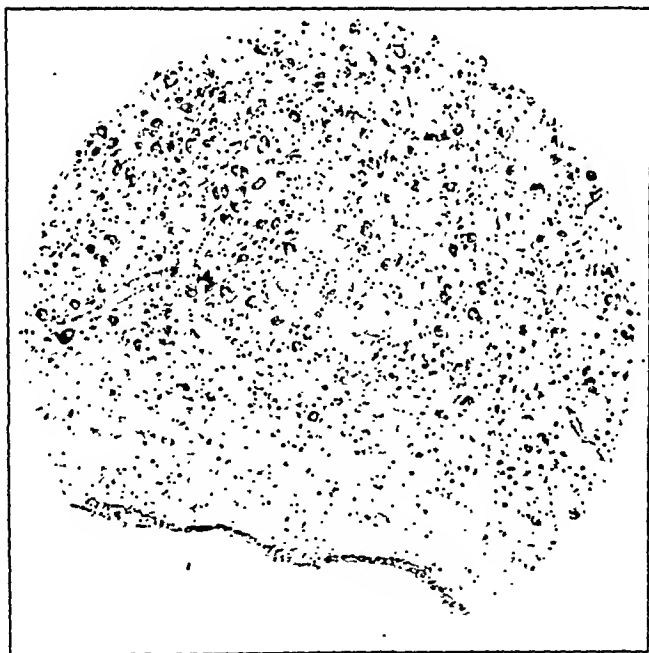


FIG. 4.—Case 3. Paraventricular nucleus of the tuber showing dilatation of the vessels and swelling of the endothelium. There is loss of many of the large hyperchromatic cells. The ependyma is proliferated. $\times 69$.

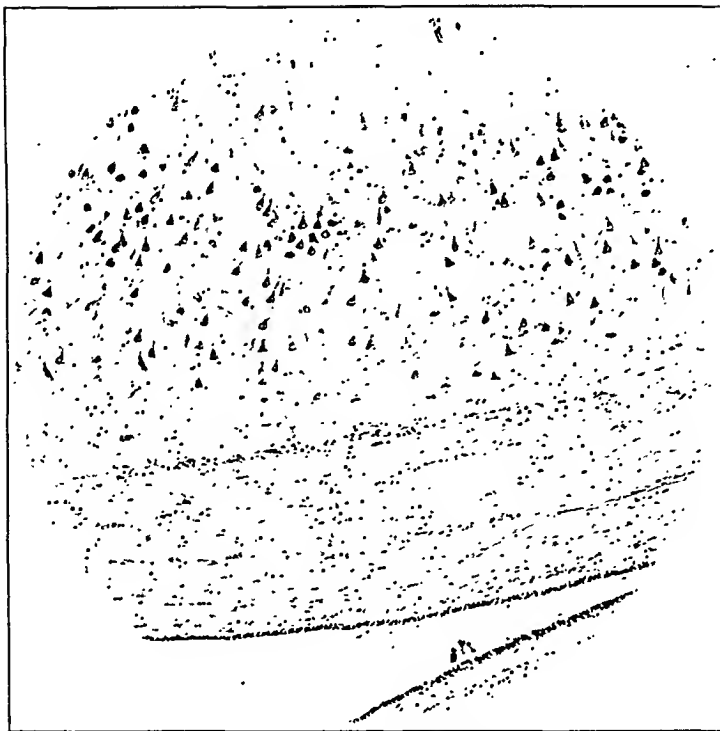


FIG. 5.—Case 5. Sommer's sector of Ammon's horn showing focal cell loss. $\times 69$.

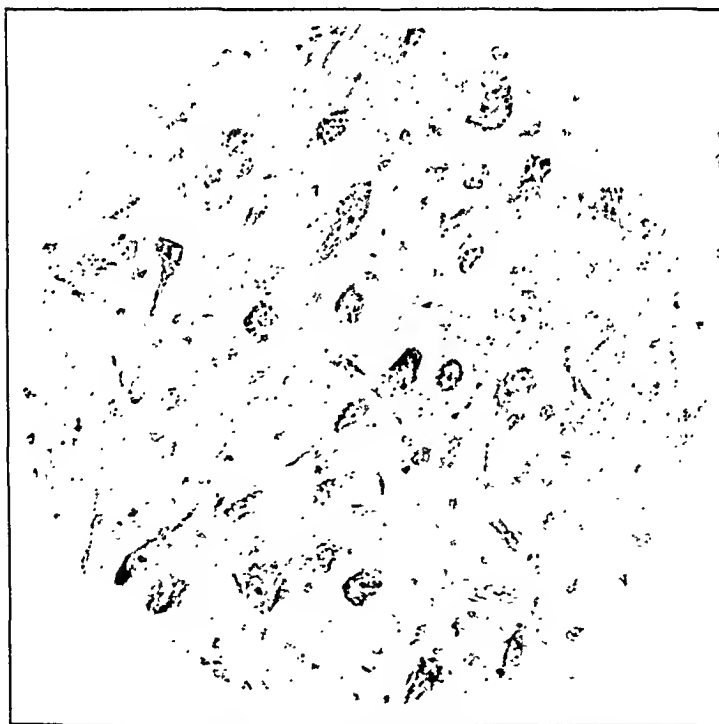


FIG. 6.—Case 2. Dorsal vagus nucleus showing cell degeneration and fragmentation. $\times 149$.

Several investigators have predicted a cerebral factor but to our knowledge no one has demonstrated a cerebral lesion or explained its physiologic *modus operandi*.

We have studied 8 cases in which no adequate gross pathologic cause of death could be found; all were without demonstrable infection; the diabetes was of comparatively short duration; and the patients were young enough to minimize the usual degenerative vascular changes.

TABLE 1.—SUMMARY OF DATA OF 8 UNCOMPLICATED CASES OF DIABETIC ACIDOSIS.

Case No.	Age, color, sex.	T. P. R. admission.	Final T. P. R.	Admitted.	Hours in hospital.	Duration of diabetes (months).	Mental state on admission.	Acidosis; duration on admission (hours).	Blood findings on admission.					Treatment.				Effects of treatment.	
									Sugar, mg.	CO ₂ , vol. %.	Urea N, mg.	W. B. C., thous.	Hb., gm. %.	Insulin, units.	Saline, liters.	Glucose, gm.	Soda, gm.	Sugar, mg.	Rise in CO ₂ , vol. %.
1. J. J.	35 B M	97 ² 123 24	..	1/29/30	8.5	?	SC*	24	1500	24	72	250	2.5	0	30	720	15
2. C. S.	14 W F	96 ⁵ 110 24	105 ? 34	3/8/31	96	18	SC	72	278	14	14	24.5	17.5	215	2.0	131	40	125	25
3. J. S.	45 W M	99 ³ 122 36	100 ³ 88 26	9/6/33	23	36	U*	24	748	12	23	14.5	16.0	245	3.0	90	26	242	30
4. K. D.	25 W F	97 ³ 90 16	102 110 34	9/20/33	15	?	U	24	770	14	30	20.8	16.5	400	5.0	60	26	350	26
5. J. G.	30 W M	94 ⁴ 140 40	101 102 40	7/17/34	6.5	2	U	72	428	11	..	35.2	14.9	270	4.0	160	14	581	7
6. M. J.	35 W F	101 140 40	106 ⁵ 158 34	8/10/34	10	36	U	48	720	13	30	400	3.6	290	20	600	9
7. S. J.	38 B M	97 ⁴ 96 32	101 128 20	9/18/34	3	2	U	72	682	10	65	16.3	14.6	270	2.0	0	7	1006	9
8. G. H.	36 B M	102 142 36	107 ? ?	5/16/35	2	3	U	48	1256	18	78	11.8	13.7	160	2.7	0	0	1136	8

* SC = Semiconscious. U = Unconscious.

A summary of certain clinical and chemical data is to be found in the table. Case 1 has been included, although the admission CO₂ was 24, because clinically and pathologically the picture was similar to the other 7 cases and because it stresses the fallibility of creating an arbitrary chemical figure to indicate coma and precoma.

Postmortem examination of the various organs in summary showed varying amounts of myocardial degeneration, congestion and cloudy swelling of the other organs. Our interest, however, was chiefly in the brain, of which detailed studies were made. Autopsies were performed at varying times within 24 hours after

death. All brains were sectioned immediately upon removal and dehydrated in graded alcohols. The tissue was embedded in celloidin and stained with toluidin blue, hematoxylin-eosin, and Van Gieson stains.

Description of Cerebral Lesions. In cases of diabetic acidosis, the subarachnoid space is moderately widened, the veins show dilatation and stasis with escape of both serum and cellular contents. The endothelial cells of the arachnoid are proliferated. Collagen fibers and young fibroblasts are present, as well as macrophages filled with blood pigment.

In the cortex, the capillary bed is dilated and shows degenerative changes in the endothelial cells. The small cortical vessels show similar changes with, additionally, the increase of the adventitial cells. There is perivascular edema and often masses of blood pigment in the perivascular space.

The cellular architecture is disturbed by the loss of ganglion cells, especially in foci in the third and fourth layers (Brodman). The ganglion cells, themselves, show pericellular edema, with shrinkage of the cell. The cytoplasm is shrunken, and the Nissl substance greatly reduced. The processes are pale, spikelike and often detached. The nucleus is large and granular in appearance. The nucleolus is at one pole, and is often fragmented. In the lower layers, the cytoplasm finally disappears to leave a bare, dark, nucleus with a fragmented nucleolus. There are many shadow cells and bits of cellular debris. In cases which have been in coma several days, there is accumulation of lipoids in the cells and some of the ganglion cells show sclerosis.

The cortical neuroglia is not greatly increased, although satellitosis is present and the astrocytes show small masses of yellow pigment in the cytoplasm. However, around the ventricles there is proliferation of the subependymal astroglia and the ependymal lining of the ventricles is increased with the formation of wartlike projections, especially in the hypothalamic portion of the third ventricle.

In the choroid plexus, the vessels in the tufts show extreme stasis with degenerative changes in the walls, and collagen fibers filling the space between the vessels and the epithelial layer. The epithelial cells themselves show a swollen, granular cytoplasm, and pyknotic nucleus. Many are desquamated.

In the basal ganglia the vascular changes are more intense than in the cortex. Here the dilated perivascular spaces often contain collagen fibers, fibroblasts, and occasional macrophages filled with blood pigment. This is most marked in the large subependymal veins. The effects of this tissue edema vary greatly in the basal nuclei. All the ganglion cells show acute degenerative changes, but in the globus pallidus the cells are reduced to mere shadows, often with lipid accumulation. In some of the cases where acidosis was of long duration, the vessels of this nucleus are infiltrated with

calcium salts. The cells of the substantia nigra are, for most part, reduced to masses of pigment.

The large hyperchromatic cell groups of the hypothalamus are greatly swollen, with an eccentric or partially protruded nucleus. The cell body is irregular with large isolated masses of chromatin deposited at the periphery. Lipoid accumulation is present, especially in the cells of the substantia innominata. Sommer's sector of Ammon's horn shows selective ischemic change with loss of cells.

The pyramidal pathway shows status spongiosus and great decrease in neuroglial cells. In the cerebellum, the cells of the granular layer are decreased, and the Purkinje cells, which are also reduced, present ischemic cell changes. The dentate nucleus is greatly reduced in size. The cells show a hyalin-like polychromatic cytoplasm with lipoid at one pole. The nucleus is compressed at the other pole and contains a large metachromatic nucleolus.

In the medulla, the changes in the inferior olive parallel those in the dentate nucleus. The dorsal motor nucleus of the vagus shows greater cell degeneration than the other nuclei of the floor of the fourth ventricle. Some of the cells are entirely fragmented, others are covered with melanotic pigment; the capillaries are very numerous and widely dilated and the perivascular edema is marked. The extramedullary roots of the vagus show proliferation of Schwann cells and of perineural connective tissue.

Summary of Pathologic Brain Changes. In brief, the brain in fatal diabetic acidosis shows lesions like those seen in acute asphyxia. The primary pathologic changes occur in the cerebral capillary bed. The capillaries are dilated, and the endothelial cells show degenerative changes with increased permeability of the walls as evidenced by the presence of perivascular and pericellular edema.

As a result of the cerebral edema there is proliferation of neuroglia, especially in the subependymal and marginal areas, and acute degenerative changes in the ganglion cells. The capillary changes are identical throughout the brain, but the degree of cellular destruction varies in different localities. The degeneration of the ganglion cells is greatest in the third and fourth cortical layers, in the extrapyramidal system, in the cerebral vegetative centers of the diencephalon and of the medulla, in the olivocerebellar system and in Sommer's sector of Ammon's horn. Because of its structural make-up, the choroid plexus is severely damaged.

Discussion. At present, we have no exact knowledge of the mechanism of production of the cerebral anoxia in diabetic acidosis. However, relying upon the results of experimental investigators, we have attempted a theoretical reconstruction of the abnormal physiology. We feel that there is cerebral anoxia, primarily based upon reduced blood volume with hemoconcentration.¹ As the result, there is marked reduction in blood pressure both systolic and dias-

tolic. This causes a reduced cerebral blood flow since it has been shown that cerebral blood flow passively follows changes in blood pressure.¹¹

Due to the absence of a vasoconstrictor mechanism in the intracerebral vascular bed,¹² stasis occurs more rapidly in the brain than in other portions of the body and leads to local anoxia of the capillary wall.⁷ This anoxia is further increased by the inability of concentrated blood to take up oxygen as readily as normal blood.⁹ Due to these factors there is an increased permeability of the capillary wall.

The increased permeability occasions cerebral edema. Once the edema is established rapid death of the cells takes place due to their intolerance of stagnant tissue fluids,³ and their high oxygen requirements.^{2,4,8}

A variation in the susceptibility of parts of the brain to anoxia has been demonstrated in the work carried out by the U. S. Bureau of Mines, relative to the effect of atmosphere deficient in oxygen.¹⁰ In these reports the areas of the brain indicated by Chornyak as most susceptible to oxygen insufficiency are identical with those in our cases which show the greatest damage.

It will thus be seen that the reduced blood volume and hemoconcentration with resulting low blood pressure produces vascular stasis more marked in the brain than elsewhere. This, in turn, results in increased capillary permeability, transudation of fluid, pericellular edema and cellular death. It might be argued that these cerebral vascular changes are due to capillary damage by the increased acid bodies found in coma. If the lesions were specific for diabetic coma such a theory would certainly be tenable, but they are not specific for diabetic coma. Similar cerebral changes have been found here in non-diabetics of at least two types; 1, Those patients which have had an acute exsanguinating hemorrhage, and 2, cases dying from congestive heart failure. In diabetic coma, there is a reduction in total blood volume comparable to a severe hemorrhage. Electrocardiographic and pathologic evidence frequently point to severe myocardial damage associated with diabetic coma. It is our belief that the cerebral vascular stasis is initiated by the reduced blood volume, which stasis is subsequently increased as a result of myocardial failure.

We have postulated the possibility, that the cerebral lesions may be due to circulatory cerebral decompensation. It is our belief that when the cerebral lesions become irreversible, due to long continued cellular anoxia, they further embarrass cardiac function, by paralysis of the vasomotor and other vegetative centers, so that in spite of an improvement in the acid base balance, the patient dies from vasomotor collapse or from failure of respiratory or cardiac function. We are not prepared to attempt an explanation of the terminal hyperpyrexia. It is possible that it is central in origin

resulting from degenerative changes produced in the region of the hypothalamus.

Summary. 1. The clinical and chemical findings in 8, fatal, uncomplicated, cases of diabetic acidosis have been described.

2. The pathologic brain findings in these cases have been reviewed.

3. A theory for the failure of adequate treatment to produce recovery in these cases has been advanced.

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A CASE OF CAROTENEMIA AND DIABETES MELLITUS WITH NECROPSY REPORT AND ANALYSES OF LIVER FOR CARO- TENE, VITAMIN A, TOTAL FAT AND CHOLESTEROL.

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THE syndrome known as carotenemia has long been recognized and its frequent incidence in patients with diabetes mellitus noted.^{1,2,3} There is however only 1 case⁴ in the literature which

includes a necropsy report. Because of this, and the recent interest in carotene as a precursor of vitamin A, we are reporting the clinical course and postmortem findings of a diabetic patient with carotenemia.

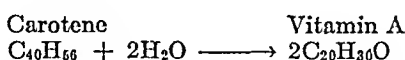
Wachenroder,⁵ in 1826, isolated a yellow pigment from carrots and named it carotin. In 1896, Baelz⁶ described a condition of pigmentation of the skin which he called aurantiasis cutis. This was due to the ingestion of mikan, a Japanese orange. In 1903, Crocker⁷ noted that "there is a xanthochromia of the skin not due to jaundice in some cases. It is more marked on the face and trunk than on the limbs, but the conjunctivæ and buccal mucous membrane are uncolored and there is no bile in the urine and feces." Although he did not state the cause, it is probable that his description referred to cases of carotenemia. The first case in a diabetic patient was described by von Noorden,⁸ in 1904, as xanthosis diabetica. It was characterized by a canary-yellow tint of the palms, soles, and nasolabial folds. He regarded a high vegetable diet as responsible and found that when the diet was discontinued the yellow color disappeared more rapidly in normals than in diabetics. Moro⁹ later described "sub-icterus" in nurslings fed on carrots and milk. Following this van den Bergh and Snapper,¹ in 1913, showed that the pigmentation in diabetic xanthosis was due to a pigment of the nature of a vegetable lipochrome. Burger and Reinhardt^{10,11} believed that the pigment was exogenous in origin and demonstrated a rise in serum carotene after a diet of green vegetables. Palmer and Eckles¹² had previously stated that the carotene of milk fat was not synthesized in the body, but was exogenous. The first description in English was by Hess and Myers.¹³ They noted coloration of the skin in infants on a diet containing carrots. Since then numerous cases have been reported.

The dietary substances thus far listed as causing carotenemia are: carrots, pumpkin, yellow squash, yellow turnip, parsnip, spinach, green and yellow beans, kale, orange, and eggs.

Physiologic Chemistry. The vegetable pigment carotene is a highly unsaturated hydrocarbon with the formula $C^{40}H^{56}$. There are three natural isomers: the α , β , and γ forms. In spite of considerable investigation within the past few years, the fate of ingested carotene is still open to discussion. Ahmad¹⁴ found that on a fat-free diet rats excreted 90% of the carotene fed, but there was almost complete absorption when the diet contained 10% fat. Graves and Schmidt¹⁵ found that in rats the absorption of β -carotene is largely dependent on the presence of bile acids. According to Drummond,¹⁶ carotene may be absorbed from the intestines in the form of a water soluble, diffusible complex with bile acids. In the blood a double colloidal phenomenon is involved (Palmer¹⁷). First there is a colloidal adsorption of carotene by albumin and second a colloidal solution of the albumin in plasma. This theory was

based on the fact that carotene could not be extracted directly from plasma. This has since been partly contradicted by van den Bergh and Muller¹⁸ who found that a colloidal aqueous solution of carotene will act similarly.

That carotene is converted to vitamin A and will cure the symptoms of A deficiency has been shown by Moore¹⁹ and others. The chemistry of this conversion is apparently a hydration of the central double bond of the carotene molecule—



The α , β , and γ isomers have the values 1–2–1 as sources of vitamin A. The actual mechanism of the conversion is unknown. Some workers have suggested an enzyme in the liver,^{20,21} but other workers have been unable to confirm these results.²²

Carotene in excess of the amount which the liver is capable of converting to vitamin A is either destroyed or excreted. Although both Hess and Myers¹³ and Wells and Hedenburg²³ reported that after carotene injection the urine became a darker yellow, it is probable that the deeper color was due to impurities in the carotene resulting from the method of extraction rather than to carotene itself. Palmer²⁴ found carotene in human milk fat. De Buys²⁵ reported the case of a mother on a high vegetable diet whose milk was a deep orange color and whose children were born pigmented and remained so until after weaning. Carotene has also been demonstrated in cerumen.²⁶

The chief means of excretion is apparently through the sweat. Miyake²⁷ stated that in cases of carotenemia the pigment was distributed around the sweat pores, and that the sweat gland apparatus was more intensely pigmented than other skin structures. Experimentally, Ansai²⁸ found that in rats the pigment was excreted in the sweat and then absorbed by the horny layer of the skin. The horny layer is thickest on the palms and soles, which are usually the most pigmented parts of the skin in carotenemia.

We are reporting the clinical course and postmortem findings of a diabetic patient who developed carotenemia and later died of acute intestinal obstruction:

Case Report. B. R., a single white male, aged 45, laborer by occupation, was first admitted to the wards of this hospital on January 29, 1934. His family history was significant in that his father had died of diabetes mellitus at the age of 74. His only previous disease was measles in childhood. Although he had lost 50 pounds in the preceding year, his complaints of polydipsia, polyuria, and polyphagia had been present only 1 month. Physical examination revealed an emaciated, weak, listless male, weighing 115 pounds. There was a pronounced acetone odor to the breath but no hyperpnea. He was dehydrated. The heart sounds were normal, rate 80, rhythm regular with occasional premature contractions. The blood pressure was 154/108. The blood count was within normal limits. The urine on

admission was colorless, specific gravity 1.030, glucose 3.5%, acetone and diacetic acid marked. The patient was treated with insulin and infusions of glucose and saline and was acetone-free in 8 hours with a blood sugar of 160 mg. % after having received 290 units of insulin, 300 gm. of glucose, and 4 liters of a normal saline solution. His diet and insulin requirement were then adjusted and he was discharged on March 20, 1934, on a diet of carbohydrate 200 gm., protein 75 gm. and fat 85 gm. and 30 units of insulin daily.

He attended the clinic irregularly and re-entered the hospital on July 26, 1934, with a history of having omitted insulin and broken his diet for 1 month. His weight had decreased 94½ pounds. His urine contained glucose and ketone bodies. He was again readjusted as to diet and insulin, his weight increased to 110 pounds, and he was discharged on August 30, 1934, on a diet of carbohydrate 300 gm., protein 105 gm. and fat 118 gm., with 30 units of insulin daily.

He again failed to attend the clinic regularly and re-entered the hospital on November 21, 1934, weighing 91 pounds, in mild ketosis and with nutritional edema. He was given a diet of carbohydrate 300 gm., protein 70 gm. and fat 85 gm., with 80 units of insulin daily. In addition, carotene was given as a source of vitamin A. Before the administration of carotene his blood serum carotene averaged 0.242 mg. % (method of White and Gordon²⁹). He received a total of 255 cc. of a 0.3% solution of carotene in oil over a period of 62 days. At the end of this time the serum carotene had risen to 0.688 mg. %. After 41 days, with a serum carotene of 0.540 mg. % the palms of the hands and soles of the feet became yellow and there was a faint diffuse pigmentation of the head. This coloration persisted during the whole period of observation, which extended up to 2 weeks after the cessation of carotene administration. He was discharged on May 2, 1935, in excellent physical condition, being sugar and acetone free and having gained 34 pounds.

He was brought into the hospital on May 6, 1935, in a stuporous state, acutely ill, in shock, and in marked ketosis. The abdomen was rigid. The urine contained glucose, acetone and diacetic acid; the blood sugar was 500 mg. %; the CO₂ combining power was 8 volumes %; and the blood non-protein nitrogen was 100 mg. %. The white blood count was 46,100 with 85% neutrophils. He was treated with insulin and infusion and clyses of glucose and normal saline, and received a transfusion of 500 cc. of whole blood. In 14 hours his urine was acetone-free; the blood sugar was 143 and the N.P.N. 75 mg. %; the CO₂ combining power was 35 volumes %. His condition was greatly improved. The white blood count had fallen to 10,150 with 86% neutrophils. However, his abdomen was still rigid and distended. The patient now vomited for the first time, and the vomitus gave a markedly positive benzin reaction. The temperature had risen to 102° F. A diagnosis of intestinal obstruction was made and laparotomy advised.

At operation the obstruction was found to be due to a Meckel's diverticulum and a Mickulicz ileostomy was performed. The patient died 9 hours postoperatively.

AUTOPSY (48 hours postmortem). We are indebted to the Pathological Laboratories of Bellevue Hospital for the autopsy report. The positive findings were: Adhesions about a Meckel's diverticulum with localized peritonitis. Immediately above the aortic ring and extending for several centimeters were small, irregular, raised areas, 2 to 4 mm. in diameter. These plaques were a deep orange-yellow color except for small yellowish-white centers. The intima for the most part was normal. In the abdominal, and to a lesser extent in the thoracic aorta, were many similar small plaques relatively isolated. The superior mesenteric artery presented an unobstructed lumen in its proximal portion with several non-elevated orange-

yellow intimal plaques. About $2\frac{1}{2}$ cm. from the origin of this artery, there was one plaque measuring 2 cm. in length, $\frac{3}{4}$ cm. in width, and 3 to 4 mm. in depth. The proximal portion of this plaque was covered by endothelium but the distal half presented a tapering extremity which projected freely into the lumen of the vessel, unattached to the underlying intima.

The liver weighed 1800 gm. and showed fatty changes. The fat in the mesentery of the small intestine exhibited many irregular sharply defined areas colored orange-yellow in contrast to the surrounding light yellow of the normal fat. This change was limited to the fat of the mesentery of the small intestine and was not present in the retroperitoneal or subcutaneous fat.

Microscopically the liver showed no abnormal pigmentation. Fat globules were present in about 80% of the polygonal cells. The cytoplasm of many cells showed vacuolated areas which did not stain with Sudan III. Glycogen was present only in small amounts as determined with Best's carmine stain.

Section through the large plaque in the superior mesenteric artery revealed a large intimal plaque lying in a trough formed by a wavelike depression of the media and adventitia. The plaque consisted of a superficial portion of dense connective tissue and a deeper vacuolated area containing many acicular spaces. Fat stains revealed extensive fat deposits in the deeper half of the plaque.

The liver was analyzed for vitamin A by the method of Davies³⁰ and for carotene by colorimetric comparison against Lovibond yellow glasses. Table 1 shows the content of vitamin A and carotene as compared to findings in other cases. Table 2 gives the liver fat in this case.

TABLE 1.—ANALYSIS OF LIVER FOR VITAMIN A AND CAROTENE IN CASES OF DIABETIC AND NON-DIABETIC INDIVIDUALS AS REPORTED BY OTHER OBSERVERS AND IN THIS CASE.

(Lovibond Blue Units Represent Vitamin A; Lovibond Yellow Units Represent Carotene).

A. Blue units per gram of liver tissue:				
	Moore. ³¹	Wolff. ³²	Ralli. ³³	This case.
Diabetes mellitus	1160	484	414	1317
Non-diabetic	282	206-245	356	

B. Yellow units per gram of liver tissue:			
		Ralli. ³³	This case.
Diabetes mellitus		29.9	39.2
Non-diabetics		10.1	

TABLE 2.—LIVER FAT AND CHOLESTEROL.

Total lipid* gm. %	11.700
Unsaponifiable fraction gm. %	0.552
Total cholesterol† gm. %	0.296
Cholesterol esters gm. %	0.088
Free cholesterol gm. %	0.208

* The total lipid and unsaponifiable fractions were determined on an alcohol-ether extract of the wet tissue—the total lipid being the petroleum ether soluble fraction.

† The micro-gravimetric method of Man and Peters³⁴ was modified for application to tissue lipids.

Discussion. Gordon, Connor and Rabinowitch⁴ reported the postmortem findings in a diabetic who had had a yellow-colored skin for 14 years. At autopsy the vertebral arteries contained large golden yellow nodules. The arteries of the circle of Willis showed a

severe degree of arteriosclerosis and were a bright yellow color. Microscopic examination of these vessels showed changes similar to those observed in our patient. Our case, in addition, had yellowish deposits in the mesenteric fat.

The occurrence of a high blood carotene in diabetics has been reported by Brandaleone and Ralli.³ They found the average fasting level in normals .109 mg. % and in diabetics .262 mg. %. The source of this increased blood carotene is a matter of speculation. Palmer³⁵ has said that "even a diabetic could not show a xanthosis unless his diet contained carotinoids." Another explanation for the increase in blood carotene in diabetics has been suggested by previous investigations from these laboratories.³³ This explanation points to the possibility of an interference in the conversion of carotene to vitamin A by the liver. In the analyses of the livers of 8 diabetics and 13 non-diabetics³³ for vitamin A and carotene, it was found that the carotene content was higher in the diabetic individuals. If ingested carotene accumulates in the liver, due to a diminished ability on the part of that organ to convert it to vitamin A, a rise in blood carotene might result because of the consequent inability of this organ to absorb as much carotene from the blood. Another explanation for the accumulation of carotene in the liver might be a failure to destroy the pigment. To a certain extent the pigment is destroyed in the body, but there is no proof of where this destruction takes place.

Rabinowitch² found a high blood carotene associated with an increase in blood cholesterol in diabetics. The figures of other workers³³ do not entirely confirm this and Boeck and Yater³⁶ found no relation between xanthosis and blood fat. It might be, however, that since carotene is handled by the body in much the same manner as the fats, that with a disturbance of the metabolism of carotene the excess would be found in the fat deposits. The orange-colored deposits in the mesenteric fat observed in this case and the intensely yellow color of the arterial plaques in both cases support this suggestion.

Summary. The case of a 45-year-old white male with a history of diabetes mellitus of 2 years' duration is reported. Prior to the administration of carotene the blood carotene was higher than normal. Following the administration it rose to a level of .540 mg. % and at this level clinical evidence of carotenemia was observed. Postmortem examination revealed deposits of carotene in the mesenteric fat and in the arterial plaques.

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ARTERIOSCLEROSIS IN YOUNG DIABETICS.

A METHOD FOR ITS RECOGNITION BY ARTERIAL ELASTICITY MEASUREMENTS.

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It is a commonly accepted clinical observation that the peripheral arteries of diabetics are more susceptible to the development of arteriosclerosis than are those of non-diabetics. This observation has been confirmed by the finding of extreme sclerotic changes in vessels of extremities amputated for diabetic gangrene and by the visualization of peripheral arterial calcification by Roentgen ray.

Autopsy studies show further that approximately 100% of diabetics dying after 40 years of age have some evidence of vascular sclerosis, and that at least 50% of all diabetics die as a result of cardiovascular complications. The high incidence of cardiovascular disease can be explained by modern advances in treatment and improvement in dietary régime whereby the life of the diabetic is definitely prolonged, or, as a writer on the subject has recently stated, "the diabetic now lives long enough to develop cardiovascular disease."

It is interesting then, to inquire when arteriosclerosis has its inception in the life of the diabetic. Does it manifest itself early in the course of the disease, irrespective of the age of the diabetic, or does it appear only as a late manifestation particularly in older diabetics who are already in the arteriosclerotic age? A knowledge, therefore, of these factors is extremely important, because if the span of life of the diabetic is to approach that of the normal, premature arteriosclerosis much be prevented. On the other hand, if arteriosclerosis is already present, the management of the patient should be such as to prevent, if possible, further development of the degenerative process.

Recent work indicates, not only that arteriosclerosis is a common complication in the elderly diabetic, but also that it may develop prematurely in young diabetics. This has been ascertained by various procedures. Warren,² in a study of 72 autopsies upon diabetics of 40 years of age and under, noted tissue changes secondary to arteriosclerosis in 50% of the cases. Joslin³ and Shepardson,⁴ separately, found by Roentgen ray examination, a relatively high incidence of vascular sclerosis in the lower extremities of a large number of young diabetics. Further confirmation of the existence of premature arteriosclerosis in young diabetics has recently been established by Rabinowitch, Ritchie and McKee,¹ who studied by statistical methods the relationship of cardiovascular disease to the age of diabetics and to the duration of the disease. In compiling their data, not only did they employ the Roentgen ray technique for studying calcification of the bloodvessels of the lower extremities but also they searched for evidence of arteriosclerosis by examining the retinal vessels, by determining roentgenographically the size of the cardiac shadow, and by utilizing other clinical procedures, *e. g.*, blood-pressure determinations, palpation of the radial vessels and auscultation of the heart sounds.

The problem of arteriosclerosis may also be investigated by measuring the degree of vascular sclerosis in terms of arterial elasticity or arterial rigidity. For the purpose of this study I recorded the elasticity of bloodvessels in 22 diabetics, all of whom were under 35 years (Table 1); 18 were 20 years and under; the youngest diabetic recorded was 6 years of age (average, 16 years). The duration of the diabetes ranged from 3 months to 6 years, with the exception

of 1 case in which the patient gave the history of having had the disease for a period of 8 years (average about 3 years). All were receiving insulin and could be classified as moderately severe diabetics with one exception in which the condition was mild. Two had been admitted to the hospital on 3 different occasions, each time in a state of diabetic coma. The blood pressure readings in all cases were normal.

TABLE 1.—ARTERIAL PULSE WAVE VELOCITIES IN DIABETES.

No. of cases.	Age.	Sex.	Radial pulse wave velocity (meters per sec.).	Aortic pulse wave velocity (meters per sec.).	Duration of diabetes.
1	6	M	5.5	..	3 years
2	10	F	6.15	4.64	5 years
3	10	F	5.43	5.26	2 years
4	11	M	5.7	..	1 year
5	11	M	6.0	4.0	2 years
6	12	F	5.52	4.05	2 years
7	12	F	5.7	4.3	5 years
8	13	F	7.0	5.1	2½ years
9	14	F	6.6	6.0	3 years
10	14	M	7.96	5.03	3 years
11	15	F	7.1	6.2	4 years
12	16	M	6.45	4.7	4 years
13	17	M	7.1	4.1	5 months
14	17	M	6.44	4.85	6 years
15	17	M	6.32	4.39	¼ year
16	17	F	9.04	5.16	5 years
17	18	M	6.04	..	½ year
18	20	M	..	5.6	8 years
19	22	F	6.08	..	¾ year
20	26	M	6.3	..	1 month
21	27	F	6.42	5.45	4 years
22	34	M	8.3	6.89	5 years

In a previous communication, I⁵ pointed out that arterial elasticity or arterial rigidity can be evaluated by determining the rate at which the pulse wave is propagated through the arterial tree, inasmuch as it is not possible to measure arterial elasticity directly on the living subject. Since the velocity with which the pulse is transmitted along arteries depends on the elasticity of the vessel walls, one can obtain an index of the degree of arterial rigidity or arterial elasticity by determining directly the velocity of the pulse wave in living man. Bramwell and Hill,⁶ after mathematical treatment of the equation relating the velocity at the front of the pulse wave to the coefficient of volume elasticity, have shown that the velocity of the pulse wave is a direct function of arterial rigidity, or an inverse function of arterial elasticity. Thus an increase of velocity of the pulse wave implies an increase in arterial rigidity, or, conversely, a decrease of arterial elasticity. By the employment of an optical recording apparatus I⁵ studied the velocity of the pulse wave through the aorta and iliac vessels (velocity of the aortic pulse wave) and through the brachial, radial and carotid vessels (velocity of the radial pulse wave) in a series of 553 normal cases, and was

thus able to establish a mean normal pulse-wave velocity value for various age groups ranging from childhood to old age.

The mean normal pulse-wave velocity values for the various age groups are graphically represented in Figures 1 (velocity of the radial pulse wave) and 2 (velocity of the aortic pulse wave) in the form of point-to-point curves for 5- and 10-year intervals (center line). The outer lines were drawn according to one standard deviation above and below the mean pulse-wave velocity for each age period. Hence, by the definition of the standard deviation, 16% of the normal cases should fall above the upper line and 34% between the upper and center line. It is therefore possible, by plotting

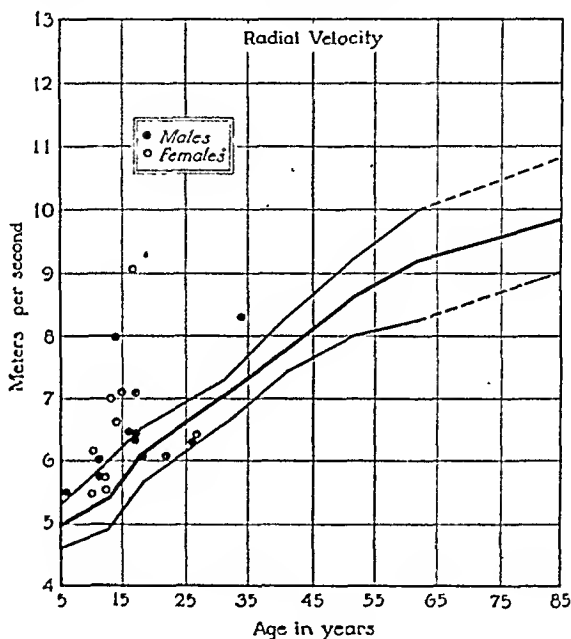


FIG. 1.—Velocity of the radial pulse wave. Graph showing the mean normal curve (center line) and the normal zones of variability (drawn according to one standard deviation above and below the normal mean). The dots indicate the velocity of the radial pulse wave (expressed in meters per second) of 21 young diabetics.

values for velocity of pulse waves on these normal standards, to evaluate the effect of various vasenlar pathologic states upon arterial elasticity. When the radial velocities for the 21 cases of diabetes were plotted on the standard graph (Fig. 1) 12 cases fell above the upper line where only 3 were expected, 9 fell between the upper and lower line where 14 were expected and none fell below the lower line where 3 were expected. According to the Chi-square test⁷ such discrepancies in the velocity of the radial pulse wave could not occur by chance alone oftener than 6 times in 100,000. In view of this significant value it follows that young diabetics as a group have a higher radial pulse-wave velocity than the normal.

On the other hand when the aortic velocities for 17 cases were plotted on the standard graph (Fig. 2) 6 cases fell above the upper line where about 3 were expected, 9 fell between the center and lower line where about 12 were expected, and only two fell below the lower line where about 3 were expected. According to the Chi-square test such discrepancies could occur through the operation of chance alone 30 times in 100; hence cannot be considered statistically significant. Inasmuch as the trend of these values tends

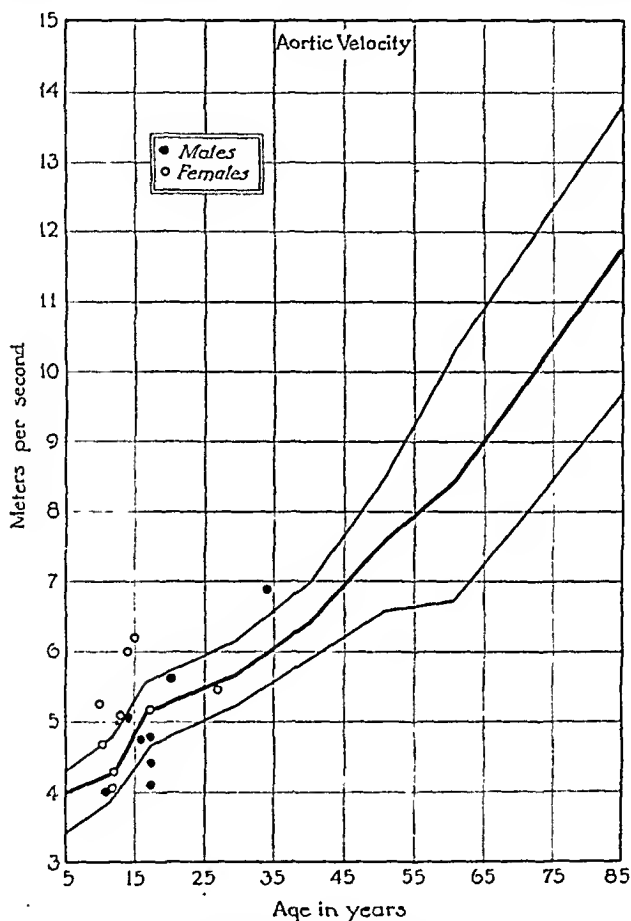


FIG. 2.—Velocity of the aortic pulse wave. Graph showing the mean normal curve (center line) and the normal zones of variability (drawn according to one standard deviation above and below the normal mean). The dots indicate the velocity of the aortic pulse wave (expressed in meters per second) of 17 young diabetics.

toward higher velocities, it is probable that if more cases had been recorded the results would also have been more definitely significant. However, until this can be statistically verified, the effect of diabetes on the elastic arteries such as the aortic and iliac vessels must remain an open question.

Comment. It is apparent from this study that an increase of arterial rigidity or, conversely, a decrease of arterial elasticity in the medium-sized arteries, may accompany the diabetic

state, and that this abnormal decrease of arterial extensibility manifests itself unusually early in the course of the diabetic's life. This is of particular clinical significance when one takes into account the fact that all patients studied in this series have not yet reached the age when arteriosclerotic changes were to be expected. The assumption, must, therefore, be advanced that diabetes predisposes the vascular system, perhaps by some morbid metabolic derangement, to the development of premature arteriosclerosis, and in consequence, stiffening of the arterial wall.

The results of this study are supported by findings of other writers who have investigated the problem by various methods. As already mentioned, Shepardson⁴ found by roentgenologic study of arteries of the lower extremities evidence of arteriosclerosis in 36% of 50 diabetics, the average age being 23.4 years and the average duration of the disease being 6.9 years. Joslin³ by a similar technique found evidence of arteriosclerosis in diabetics 50 years of age and under in 15.4% of his cases who had had diabetes for a period less than 5 years, and in 57.2% of his cases who had had diabetes for more than 5 years. In the study by Rabinowitch and his co-workers¹ of a large group of diabetics by various methods, previously mentioned it was found that of 162 individuals of 50 years of age and under who had had diabetes for 5 years or less, vascular disease was found in 64 cases, or an incidence of approximately 39%.

In the present study the findings appear particularly significant when one considers that the average age of the 22 diabetics recorded is 16 years and the average duration of the disease is slightly more than 3 years.

The results of the above studies justify the conclusions that arterial hardening appears prematurely in young diabetics. At the present time there is no definite evidence available to indicate why an increase of arterial hardening occurs prematurely in some diabetics and not in others. If this etiologic factor were known it would be of inestimable value in controlling and possibly eliminating the development of premature arterial aging in the diabetic, but until further evidence is forthcoming the idea must be accepted that every young diabetic is a potential arteriosclerotic. To combat the development of arteriosclerosis in diabetes several investigators (Joslin, Rabinowitch, Geyelin, Shepardson) have advocated the high carbohydrate and low-fat diet as opposed to the high-fat diet on the theory that diabetics who are on a high-fat diet develop a hypercholesterolemia, the presence of which may be an important factor in the production of vascular sclerosis. Whether the high-carbohydrate and low-fat diet will be effective in preventing arteriosclerosis or holding it in abeyance, however, remains to be ascertained by further studies. But regardless of what therapeutic measures are proposed to treat the diabetic it becomes apparent from this study that no treatment can be regarded as successful

unless it has become effective in checking the development of arteriosclerosis or the progression of the disease if it is already present. Only by accomplishing this can the diabetic's span of life be increased to approach that of the normal.

Summary. The pulse-wave velocity method was utilized in studying arterial elasticity in the large and medium-sized arteries of 22 young diabetics. To test the significance of the pulse-wave velocities obtained in this study the well known Chi-square test was employed. While the values for the transmission of the aortic pulse wave did not indicate any significant changes from the normal, those for the transmission of the radial pulse wave were definitely significant.

Conclusion. The diabetic state either initiates early or accelerates the development of premature arteriosclerosis in the young adult.

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THE METABOLISM OF LEVULOSE.

VIII. THE INFLUENCE ON TOLERANCE OF CERTAIN NON-ENDOCRINE DISORDERS.

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In a series of earlier papers certain aspects of the metabolism of levulose in humans have been reported, dealing severally with some general considerations,¹ the influences of hepatic dysfunction,²

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the levels of ovarian activity,³ and the phases of the reproductive cycle.⁴ Determinations have been made simultaneously of the effects of these various agencies on the utilization of pure galactose; these observations have served as controls, previous studies^{5,6,7} having established criteria of usual performance. While both sugars are governed broadly by the general provisions of carbohydrate utilization, such as transformation to glycogen and ultimate oxidation to carbon dioxide and water, the earlier studies have clearly demonstrated that there are certain highly significant differences in the several mechanisms of the intermediate metabolism of these two sugars. The present paper deals with an extension of the earlier investigations to include a number of morbid states all unassociated with the endocrine system and all of which are generally recognized as influencing directly or indirectly the utilization of carbohydrates by the human body.

Method. In view of the more detailed statements of the previous papers, only brief reference need be made to the methods of study. Individuals presenting one of the conditions under investigation were hospitalized and thoroughly studied for a period of not less than 1 week. This served not only to document the presence of the primary condition with adequate objective evidence but also to evaluate the possible coexistence of other secondary conditions which might independently influence the results of the study. This is of vital importance, particularly when the criterion of function level is no more than an end result susceptible to the influence of a wide variety of seemingly unrelated agencies. So far as possible, cases were selected which were demonstrably free from disturbing complications. In a few instances this general provision was abrogated to include some individual whose condition was of especial interest; all such cases will be noted in the body of the report.

Sugar tolerances were estimated by a modified Hofmeister⁸ technique, for reasons previously discussed. Ten-gram gradations, as usual, were selected for the galactose test meals, while 25-gm. stadia were regarded as more appropriate for levulose with its significantly higher tolerance limits. The usual precautions as to adequate preliminary feeding for a period of days, basal state at time of testing with control of exercise and temperature, were rigorously observed.

Levulose was tested for qualitatively by the methods of Benedict and Seliwanoff, while the quantitative estimation involved a combination of the Benedict titration, Folin-Wu procedure after the use of Lloyd's reagent, the precision polariscope, and the use of controlled fermentations with washed yeast. The full analytical details are reserved for a later communication.

The composition of the study series together with a few descriptive details is presented in Table 1.

The present liver group is drawn only in small part from that earlier discussed,² cases with significant complication being largely excluded. Three of the series had histories of earlier neural damage

consisting severally of a fractured spine, hydrocephalus and a possible encephalitis; none of them gave current evidence of organic lesion at the time of examination. In addition, there was 1 case of treated syphilis with negative serologic tests but a positive gold curve in the spinal fluid. The hepatic status was defined by the summation of evidences derived from the history, physical examination, icteric index, van den Bergh, duodenal function (McClure), blood and urine studies, and the radiologic examination of the gall-bladder (Graham).

TABLE 1.—COMPOSITION OF SERIES.

Subgroup.	Sex.			Age (yrs.).		
	Male.	Female.	Total.	High.	Low.	Average.
I. Hepatic dysfunction	10	30	40	71	13	34.2
II. Syphilis	6	10	16	66	5	34.6
III. Neural disorder	4	16	20	54	9	24.7
IV. Blood dyscrasia	8	4	12	73	20	53.7
V. Malignant neoplasm	8	2	10	65	15	49.5
VI. Infection	5	5	10	13	8	11.0
Total	41	67	108			

Five of the syphilitics were of congenital origin with characteristic physical stigmata supplementing the usual objective evidences. Practically all of the group had received extensive treatment but half of them still gave positive serologic response. One patient had an earlier history of head trauma but neurologic examination failed to disclose evidence of residua certainly attributable to it.

The group with neural disorders was highly diversified. One-half of the composing members had a traumatic background; there were 3 sisters with Friedreich's ataxia, single cases of diabetes insipidus, hydrocephalus, cord tumor, and postmeningitic and encephalitic conditions. All were carefully studied neurologically. Three were achondroplastic dwarfs.

The blood dyscrasias were also diversified, with 7 cases of primary anemia together with 2 of lymphatic (32,000 and 58,000 leukocytes) and 1 of myelogenous (1,236,000 leukocytes) leukemia, and 1 each of polycythemia (11,060,000 erythrocytes) and chlorosis. The anemias gave characteristic blood pictures, positive neurologic findings, and presented achlorhydria and negative response to neutral red. One diagnosis was further confirmed at autopsy. One of the lymphatic leukemia cases gave a positive duodenal function test indicating disturbance of biliary production, implying a degree of hepatic dysfunction.

The cases in the malignant group comprised 2 patients with Hodgkin's disease; the others all had neoplastic growths, primary in the stomach, prostate, larynx, pancreas and breast. Several had secondary metastases—in 2 instances to the liver—and 1 breast cancer was recurrent. One testicle case had been operated seemingly with success and, as will be shown later, had the only normal

galactose tolerance in the group. One of the throat cases had been earlier treated for lues; the current serologic tests were all negative.

The final group was composed chiefly of children with both badly infected tonsils and sinuses. An acute appendicitis presented in 3 of these and they were discharged for operation.

Except as indicated above, subversive complications were absent, and in a number of the positive reports significant current involvement could not be demonstrated.

The females are in ratio of 3 to 2 in the total group, a somewhat higher masculine proportion than that usually encountered. Exception is noted in the cancer and blood groups, in which also no children appear. The basis of the case selection renders the fact of no significance but prevents the sex factor, if any,* from playing a considerable rôle in the sugar study. The age scatter is a wide one in all but the last subgroup. The average ages reflect in some measure the primary conditions of the etiologic classification.

Blood and urine data are germane to the consideration of sugar metabolism even though glucose be the usual carbohydrate measured.

TABLE 2.—BLOOD AND URINE DATA.

Subgroup.	Urine, glyco- suria + (%).	Blood sugar (mg.).		
		High.	Low.	Average.
Hepatic dysfunction	20	106	69	93
Syphilis	31	117	75	95
Neural disorder	10	107	78	90
Blood dyscrasia	8	118	84	94
Malignant neoplasm	20	113	85	96
Infection	0

Only the children of Group VI fail to show at least 1 case of glycosuria. One-fifth of the hepatic and one-third of the luetic groups present this evidence of disturbed carbohydrate metabolism, the figures comparing well (23% and 25%) with those deriving from much larger groups previously reported.⁹ The other comparisons—malignancy 40%, blood dyscrasias 19%, and neural lesions 25%—show a less frequent incidence in the present series. So far as the metabolism of glucose may be equated with that of the other sugars this feature is desirable, as departures from the normal by the sugars under investigation gain an added significance. The blood sugars show nothing remarkable, both the range and average values falling within the conventional limits of the normal. Exception might possibly be made to the inferior limits in Groups II and III. These were single cases and the sole exceptions to an otherwise complete conventional normality.

Before discussing the sugar tolerances as actually observed, brief

* It seems very doubtful if there be a sex difference in the metabolism of levulose. See earlier citation.²

consideration must be given to the criteria of normal performance. These are collected in Table 3.

With the sex difference and the fluctuations in the levels for the female seemingly intrinsic in her degree of sexual maturity, data can be equated in a mixed series only by recording tolerances in terms relative to the normal standard for each individual. Galactose tolerances, for this reason, are reported as normal or as percentile deviations, indicating both direction and degree of departure from the norm.

TABLE 3.—NORMAL TOLERANCES. *

Galactose (gm.).	Female.	Levulose (gm.).*
20	Prepuberal	75 to 100
20 to 40	Puberal	75 to 100
40	Adult	100 to 125
40 to 30	Postmenopausal	100 to 125
	Male.	
30	Child	75 to 100
30	Adult	100 to 125

* Values as given are approximate but conform to present data.³

Six of the liver group are at normal levels; the remainder exhibit varying degrees of depression. Further investigation of the 6 cases which conform to predicted tolerance shows that 4 of them are renal cases with definitely lowered renal permeability. The opinion has been expressed^{10,11} that this condition retards the elimination of sugar and thus raises the apparent tolerance level; our own experience is broadly confirmatory to this postulate. The remaining 2 cases gave some evidence of renal involvement though not of sufficient magnitude to be considered in this connection. In addition, as one of us has shown elsewhere,⁵ a small percentage of uncomplicated liver cases demonstrate an increased tolerance for galactose. This certainly implies that an occasional case could fall between the abnormal extremes and show a normal level.

TABLE 4.—GALACTOSE TOLERANCE.

Subgroup.	Deviation.					Average (%).
	Above normal.	Normal.	Below normal.			
			±0 to -25.	-26 to -50.	Over -50.	
Hepatic dysfunction	0	6	2	18	14	-46
Syphilis*	1	2	1	7	4	-37
Neural disorder†	0	2	1	10	5	-47
Blood dyscrasia	1	0	1	4	6	-46
Malignant neoplasm*	0	1	0	2	6	-54
Infection	0	3	0	5	2	-33
Total	2	14	5	46	37	

* One case not tested.

† Two cases not tested.

Syphilis shows a definite downward trend but not of marked degree. One case is above prediction, a man, aged 42, with cardiac disease but nothing in the diagnostic pattern to account for the anomaly. The 2 cases with normal tolerance were both nephritides.

A cardiorenal status offers possible explanation for 1 of the 2 neural cases with normal tolerance; the other was a child, aged 10, with a history of severe head trauma but with a negative neurologic examination.

The sole case in Group IV with abnormal response to galactose was a woman, aged 73, with primary anemia and a significantly impaired renal function. The normal cancer case has already been noted—a testicular tumor which had apparently been successfully operated and from which there were no demonstrated residua.

With the relatively slight influence exercised on carbohydrate metabolism by infective processes that do not acutely involve the liver, it is not surprising that several of the infection group show a normal tolerance.

Let it be noted, however, that with the exception of the few cases commented on above, the remainder of the series (85%) show a depression of galactose tolerance and in a measure best expressed by the report of the average deviation summarizing each subgroup.

Not only do these several states lower the utilization power of the organism for the customary sugar glucose, as shown by the appearance of glycosuria, but also the tolerance for galactose is significantly lowered in a very large number of the individuals presenting the several conditions under investigation.

The levulose data are collected in Table 5. Here the individual test-meal levels producing levulosuria are reported, as the normal standards are not as yet certainly defined. With the differences noted in the child and the adult, groups containing both are separated into their respective categories. This permits a tentative rough definition of normal, increased, or diminished tolerance on the basis of the standards given in Table 3. The data for the probable normals are given in heavy-faced type in Table 5:

TABLE 5.—LEVULOSE TOLERANCE.

Subgroup.	Positive test meal (gm.).						
	Over 150.	150.	125.	100.	75.	50.	25.
Hepatic dysfunction (a)	1	2	3	5	17	7	4
(c)	0	0	0	0	1	0	0
Syphilis (a)	2	1	0	0	7	2	0
(c)	0	0	0	0	1	1	2
Neural disorder (a)	1	0	1	4	3	3	2
(c)	0	0	0	0	1	2	3
Blood dyscrasia (a)	0	1	1	5	1	4	0
Malignant neoplasm (a)	2	1	0	4	2	0	1
Infection (c)	0	0	0	4	4	2	0
Total	6	5	5	22	37	21	12

Dealing with the data as they present and for the moment without reference to the equivalent galactose indications, it is evident that an appreciable number of cases with hepatic dysfunction demonstrate a normal utilization capacity. The trend with lues is unmistakably downward, but 3 of this small series report tolerances that are definitely increased. One-third of the neural group are normal or above, and over half of the patients with blood dyscrasias fall in the same categories. Malignancy produces but a very moderate depressing effect, the 3 cases below the normal being balanced by an equal number above normal prediction. Finally, only 2 of the children fall below the normal zone. While some depressing effect on levulose tolerance is manifested by each of the several conditions comprised within the study group, the influences are far less potent than in the equivalent response to galactose feeding.

This can be rendered more concrete by direct comparison. Reporting each case simply as normal, increased, or diminished, and waiving the possible greater nicety of arithmetical expression, a precision that is patently more apparent than real, the relative behavior of the two sugars can be contrasted.

TABLE 6.—COMPARISON OF DEVIATIONS.

Subgroup.	Deviations (%).					
	Above normal.		Normal.		Below normal.	
	Gal.	Lev.	Gal.	Lev.	Gal.	Lev.
Hepatic dysfunction . . .	0	7	15	23	85	70
Syphilis	7	19	13	6	80	75
Neural disorder	0	5	11	30	89	65
Blood dyscrasia	8	8	0	50	92	42
Malignant neoplasm . . .	0	30	11	40	89	30
Infection	0	0	30	80	70	20
Total	1.9	10.2	13.5	31.5	84.6	58.3

In the group of hepatic dysfunction there is a reasonable degree of correlation. Galactose utilization seems to be somewhat more uniformly depressed than that of levulose but both show the same general tendencies. This same observation applies to the luetic group, both sugars showing a lowered utilization in a majority of the cases.

In the neural group the agreement is distinctly less good. The galactose response is definitely more uniform than is that of levulose. In the blood dyscrasias there is an actual change in sign, with half of the levulose tolerances normal and only 42% depressed as against a 92% incidence of lowered tolerance in the galactose response. With the cancer group the discrepancy is even more marked, while in the last series 80% show a normal levulose and 70% a depressed galactose tolerance.

The differences in the intermediate metabolism of the two sugars, touched upon briefly in the opening paragraphs, here finds marked expression. In the last three subgroups and tendentially at least in the third, there is a lack of agreement in the behavior of the two sugars that is of wholly convincing proportions. Significant as are the divergencies here manifest, an even more rigid analysis can be made by comparing the results obtained with each sugar in the individual case.

TABLE 7.—CORRELATION.

Subgroup.	Agreement (%)
Hepatic dysfunction	68
Syphilis	80
Neural disorder	61
Blood dyscrasia	42
Malignant neoplasm	33
Infection	10

In spite of the relative concordance of the reports from the liver cases when they are assembled as a group, this present more-searching approach shows that but 2 in every 3 cases agree qualitatively, and this, let it be noted, waives the more rigorous comparison which would take cognizance of the relative quantitative relations. Correlation in the lactic series is high, confirming the indications of the previous comparison. The neural group shows a somewhat less satisfactory agreement than did the hepatic series, and the remaining three subgroups show a progressive lack of concordance that becomes almost complete in the children's series (Group VI). That this is not due to any influence intrinsic in childhood can be clearly demonstrated by a review of the results with children in the other groups.

TABLE 7a.—CORRELATION OF CHILDREN'S DATA.

Subgroup.	No. of cases.	Agree.	Disagree.
Hepatic dysfunction	1	0	1
Syphilis	4	3	1
Neural disorder	6	4	2
Total	11	7	4

In other words, the children, excluding those in Group VI, show an agreement of 64%, a value concordant with the averages of the several groups in which they occur. Patently one must seek further for the explanation of the discrepancies shown by the children with infections.

Discussion. A brief review of more recent literature discloses the wide array of contradictory reports which must inevitably occur where fundamentally different methods of approach and widely fluctuating criteria of positive response preclude a common basis for comparison. The general literature has already been briefly

reviewed in the first paper of this series.¹ A few citations germane to the text may be given here.

The influence of various types of hepatic disorders upon the tolerance for each of the sugars is still a field of active controversy with a steadily growing literature. A depressing influence of syphilis on levulose utilization has been reported,^{12,13} and equally denied;¹⁴ hepatic involvement was a feature in all of these series. Hurst¹⁵ could find no abnormality of the blood-sugar curve with levulose in cases of paralysis agitans and cerebral vascular disease. The levulose response in primary anemia is reported as normal,^{16,17} that to galactose as normal,¹⁷ and to glucose as depressed.¹⁸ Leukemia had no effect on levulose¹² and was depressed in but 1 case in 7 in a second report.¹⁶ Polycythemia is reported both as a depressing influence¹³ and as one without effect¹⁶ on levulose tolerance. Malignant neoplasm does not depress the utilization of levulose¹⁹ even when the liver was involved;^{20,21} cancer of the head of the pancreas²² gave positive response in 3 cases of 5 tested. Many of the citations given above report only a very small number of cases, in some instances only 1. The papers from the Mayo Clinic^{14,16,22} form a body of valuable material, but the Tallerman²³ blood-sugar technique was used and this precludes a parity for comparison with the present studies.

To recapitulate briefly, in our own studies all of the conditions under investigation produce a downward trend in the power of the human organism to utilize galactose, a trend that assumes some magnitude in 85% of the cases. Fourteen patients show a normal tolerance with 2 more an increased tolerance. Of these, 6 are primary liver cases, possibly explicable on the basis of the sugar anomaly already noted.⁵ One neural case and the testicular cancer gave no evidence of present disturbance. Four more were established nephritics and a lowered renal permeability may, but by no means certainly does, explain their failure to follow the characteristic trend. This leaves but 4 cases in the entire group whose observed tolerances depart from the expected level and for which no plausible explanation is now forthcoming.

Turning to the levulose reports on these 16 cases, 2 of the liver and 1 with neural damage are in agreement with a normal tolerance. To these should be added 1 luetic patient whose utilization capacity for both sugars is increased. Of the remainder, 4 hepatic, 1 luetic, 1 neural and 3 from the infection group show depressed tolerances, while 1 neural and 1 cancer patient are above prediction. The sole remaining case was the woman, aged 73, with primary anemia and an established nephritis who showed an increased galactose and normal (100 gm.) levulose tolerance. One-tenth of the total levulose reports are above and one-third more are normal. The relative concordance between the two sugars in the hepatic and luetic

groups, which constitute one-half of the entire series, tends to minimize in the series summation the marked deviations characterizing the other four categories.

That the liver plays an important but not identical rôle in the metabolism of the two sugars seems probable, although, as noted above, this is still a matter of active debate. If this assumption be correct, it might be postulated that lues mediated its influence through the liver and that this was the explanation of the relative—but far from complete—concordance in these two groups. Unfortunately for so simple an adjustment, the neural involvement in syphilis is not a matter of speculation, and in the neural group the trend is toward a lack of agreement in the response of the two sugars. This finds even more certain expression in that of the blood cases. Disharmony prevails in the cancer series in which 2 cases have demonstrated and a third a probable metastatic involvement of the liver. The 3 galactose reports on these patients are of a profound and uniform depression of tolerance; the levulose, on the other hand, shows a complete impartiality with 1 increased, 1 normal and 1 slightly depressed. Certainly the postulate that the liver is the sole agent mediating these abnormalities in carbohydrate metabolism cannot marshal any adequate array of supporting evidence. In like manner, the complete absence of hyperglycemia, particularly in the cases of long standing, rules out a hormonal pancreatic influence as the controlling factor.

Once again, the only inference which seems warrantable from this latest collection of mutually inharmonious data is that in the intermediate metabolism of these two sugars a variety of mechanisms are operative, some seemingly influenced qualitatively alike, at least, by agencies common to both, and others, as in the mammary effect,³ in which only one participates. Further study with a wide variety of abnormal states of reasonably assured etiology may throw further light on the problem. For the present, nothing remains but to report the factual evidences derived by controlled experiment. In the material thus far secured may be found certain data which should help toward a final resolution of some of the contradictory reports so widely recorded in the literature.

Summary and Conclusion. In 6 groups of patients showing respectively hepatic dysfunction, syphilis, neural disorders, blood dyscrasias, malignant neoplasms, and infections, the tolerance to levulose was determined. The total series comprised 108 patients. The cases of 11 children showing hepatic dysfunction, syphilis and neural disorders are likewise reported.

The results, compared with those secured from the use of galactose as a test sugar, agreed in varying proportions from 10% in infections to 80% in syphilis. The discrepancies in the various groups are discussed.

It is concluded that in the intermediate metabolism of these two sugars a variety of mechanisms are operative, some seemingly influenced qualitatively alike, at least, by agencies common to both, and others in which only one participates.

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STUDIES ON TWO CASES OF URTICARIA FROM COLD SENSITIVITY AND OF THE EFFECT OF HISTAMIN TREATMENT.*

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THE unusual dermatologic phenomenon of localized redness, burning and edema, following the exposure of the skin to cold and occurring with or without a generalized reaction has been reported by a number of investigators (mostly European) since it was first described by Béhier¹ in 1866. Horton and Brown,^{2,3,4} Horton,⁵ Duke^{6,7} Blackford,⁸ Bray,⁹ Paul,¹³ Dobbs,¹¹ Weiss¹² and Levine¹³ have added reports of cases, with experimental observations, to the American literature since 1929. Levine has recently thoroughly reviewed the literature with a summary and discussion of the immunologic, humoral and neurovascular hypotheses of the etiology of the condition. He has included the report of 1 additional case.

Two cases of cold sensitivity are herein reported. Case 1 is more important: first, because of the unusually high temperature at which the reaction occurs, secondly, because it was possible to complete certain interesting experimental work, and, finally, because we were able to institute histamin therapy with definite improvement.

Case Reports. CASE 1.—An unmarried lady, aged 32, who was born in Austria of Jewish parentage and who has been a resident of the United States for the past 15 years, came to this clinic on July 23, 1935. Her complaints, at that time, were localized itching and burning sensations as well as throbbing headaches and generalized flushing following the exposure of an area of her skin to cold air or cold objects. Following such exposure, an area of redness and wheal formation would appear at the site exposed. She also stated that she was unable to eat ice cream or chilled food because her throat would soon seem as though it were swollen, and she would have difficulty in swallowing. In May, 1934, she had an infection of the distal phalanx of the right index finger. She consulted a physician, and the finger was incised. Neither a local nor a general anesthetic was used. The finger drained, and healing was complete in 2 weeks. She did not receive any type of serum therapy. Approximately 2 months after the finger had healed, she noticed that, as she handled cold objects or washed her hands in cold water, this same finger became swollen and red. This phenomenon did not occur on any other part of her hands at that time. A few days later, however, the same reaction occurred on her hands, arms, feet and face. Her face would become extremely swollen when exposed to the cold winter air. The same would happen when she

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carried a cold milk bottle against the skin of her arms. Her condition was as above described on admission to the hospital. With the exception of the statement that she becomes nauseated and often vomits whenever she eats egg in any form, there is a negative personal and familial allergic history. Her past history revealed only the following significant facts. She has a history of but one previous illness: 15 years ago, while crossing the ocean, she developed a cough which was diagnosed as due to bronchitis. During the winter months, for 3 years, there was a recurrence of the same condition, as there was each time she went swimming during the summer. For the past 2 years, however, she has not had an attack, but, during that time, she has not been swimming. For the past 15 years she has had a feeling of swelling in her throat whenever she has eaten ice cream. Whether this reaction would have occurred before is open to question, since she never ate ice cream until her arrival in the United States. She continued to eat it until the summer of 1935, when it produced swollen lips to such a

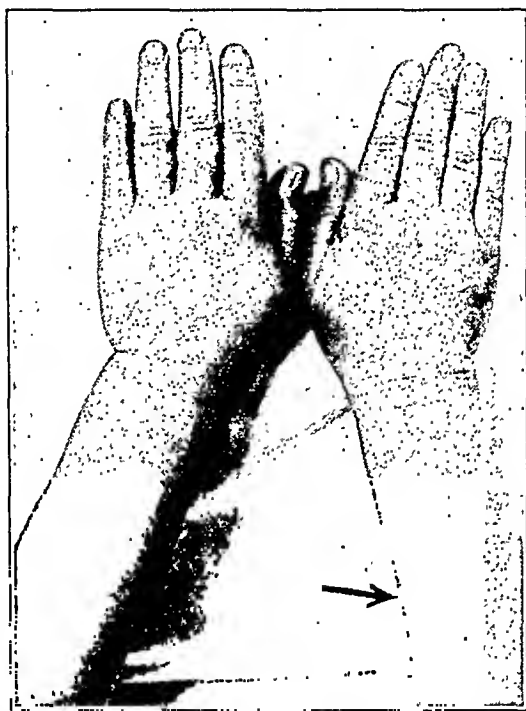


FIG. 1.—Note swelling of left hand after exposure to cold water. Note also patch of urticaria on right arm, after application of ice locally.

degree that she discontinued frozen foods in all forms. The menstrual history is normal. There has been a gradual but not an abnormal increase in weight for 3 years previous to this last year, during which it has reached a plateau. Physical examination was negative as to anything abnormal except the reactivity of her skin to cold. Laboratory reports were as follows:

Blood count: red blood cells, 5,090,000; white blood cells, 9550; hemoglobin, 96%. Differential count: neutrophils, 72%; small lymphocytes, 19%; large lymphocytes, 6%; monocytes, 3%.

Urine analysis: clear; specific gravity, 1.018; sugar, negative; albumin, negative; acid reaction; microscopic examination: epithelial cells. No hematuria, hemoglobinuria or history of same.

Blood Wassermann: negative.

Experimental Studies. *Experiment 1.* The temperature at which the reaction would take place was determined by filling a small flask with

water and applying the flask to the forearm for a few minutes. The temperature of the water was gradually reduced, and, by recording the temperature of the flask as the temperature at which the reaction occurred, the results in Table 1 were obtained. Because the results obtained in this test seemed improbable, since the temperature of the object causing the reaction was unbelievably high, it was repeated (Experiment 1a). One would expect that this patient would be in a constant state of edema as soon as the room temperature reached 24° C. (75.4° F.). This, however, actually was not true. A modification of this test showed that the reaction depends entirely upon the actual temperature of the skin, which represents a resultant of the temperature of the object in contact with it, the heat conductivity of the object, and the generation of heat by the tissues beneath the point of contact. This was demonstrated as follows: the patient, while seated in a room of 22.3° C. temperature, for over an hour had no evidence of reaction. The skin temperature of her arm was 31.4° C. A metal cabinet, which had been a permanent fixture in the room, had a temperature of 23.5° C. or 1.2° C. higher than the room temperature. The cabinet, however, seemed cold, since it removed heat from the arm more rapidly than did the air; consequently, the arm became cooler, after it had been in contact with the metal for 4 minutes, and the skin temperature at the point of contact had been reduced to 27° C. A definite redness and edema appeared at the area thus cooled.

The temperature of an object applied to the skin was gradually reduced as in Experiment 1, to determine the skin temperature necessary for the production of the reaction (Table 1, Experiment 1a).

TABLE 1.—DETERMINATION OF TEMPERATURE AT WHICH REACTION OCCURS.
Experiment 1.

Room temp., ° C.	Temp. of material applied, ° C.	Time of contact, min.	Reaction.
25	26.4	4	Negative
25	25.4	4	Negative
25	24.0	4	Redness; distinct wheals

Experiment 1a.

		Temp. of skin with material applied, ° C.		
24	32.0	31.7	4	Negative
24	26.2	30.3	4	Negative
24	25.1	28.6	4	Redness; no edema
24	24.2	27.6	4	Redness; slight edema
24	24.0	26.8	4	Redness; definite edema

Control skin temperature of arm at room temperature: 31.4° C.

Experiment 2. The blood pressure, pulse and skin temperature and changes in size following the production of the edema in one hand and wrist are noted in Table 2, Experiment 2.

TABLE 2.
Experiment 2.
RESPONSE TO REACTION.
(Hand and wrist in 8° C. water—5 minutes).

Time.	B. P.	Pulse.	Circumference of wrist, cm.	Temperatures (° C.).			
				Room.	Dorsum, hand.	Right check.	Left check.
Control	140/86	102	15.75	24.6	32.5	35.8	35.1
Ten minutes after removal	124/70	124	18.0	25.5	34.6	35.8	35.8

Experiment 3. The marked similarity of the patient's generalized response to induced cold urticaria and to histamin hydrochlorid injected subcutaneously is noted in Table 2, Experiment 2.

Experiment 3.
COMPARATIVE RESPONSE TO REACTION.
Histamin hydrochlorid 1 cc. (1 to 1000 sol.) subcutaneously.

Time.	B. P.	Pulse.	Cheek temp., ° C.
Control	146/90	92	34.2
5 minutes after histamin	132/68	135	
10 minutes after histamin	130/60	140	
15 minutes after histamin	126/76	126	36.1

Experiment 4. When a localized area of skin was exposed to cold, a very definite local vasodilation appeared, a prominent redness of the skin could be seen, and a marked increase in the skin temperature of this area resulted. This temperature rise was measured and noted in Table 3. Blood pressure and pulse readings are included.

TABLE 3.—TEMPERATURE (° C.) RESPONSE OF AREA EXPOSED.

<i>Experiment 4.</i>						
	Room.	Dorsum, hand.	Mid- arm.	3d finger.	Left cheek.	Pulse.
Control	24.6	31.3	31.6	32.2	34.3	106
Hand and wrist in water 8° C for 5 minutes						112
10 minutes after exposure	24.6	35.7	34.1	33.6	36.1	
Control.	Hand in water 2 mins.	Hand in water 3 mins.	Hand in water 5 mins.	Hand removed 10 mins.		
Blood pressure: 142/90	146/94	130/88	122/84	138/94		

Experiment 5. Bray⁹ and Levine¹³ were able to demonstrate, in their cases, local eosinophilia in a wheal produced by exposure of the skin to cold. This test was done twice on our case, but no eosinophilia appeared either time. The results are shown in Table 4, Experiment 5.

TABLE 4.—TEST OF LOCAL EOSINOPHIL RESPONSE TO COLD URTICARIA.
Experiment 5.

	I. Eosinophil count per 100 leukocytes.	II. Eosinophil count per 100 leukocytes.
Index finger before exposure	2	0
Same finger: Whole hand in edema	0	0
Half hour later	0	0
Opposite index finger: Hand not exposed	0	0
Half hour later	0	2

Experiment 6. Horton and Brown³ showed the histamin-like effect of the production of cold urticaria on the gastric acidity. This test on our case confirms their findings (Table 5, Experiment 6).

TABLE 5.—HISTAMIN-LIKE EFFECT OF COLD URTICARIA ON GASTRIC ACIDITY.
Experiment 6.

Specimen.	Free acid.	Total acid.
Fasting	43	59
Remarks:		
1. Hand in water 10° C. for 10 minutes. (Tourniquet at elbow.)		
2. Tourniquet removed in 5 minutes.		
3. Patient noted general effect, throbbing in head, 2½ minutes after removal of hand from water.		
Specimen.	Free acid.	Total acid.
10 minutes after hand was removed	78	90
20 minutes after hand was removed	92	106

Experiment 7. The Perutz, Brugel, Greenfeld reaction, in which 10% menthol in alcohol is applied to an area of the skin, and which, when positive, either produces the same reaction as does the cold or causes the area to become more hypersensitive to cold, was negative in our case. An area of redness resulted, but there was no urticaria, and the area thus treated did not show an increased hypersensitivity to cold.

Experiment 8. Cold was applied to an area previously anesthetized with 2% novocain intracutaneously and subcutaneously. In our case, an area 5 by 8 cm., over the deltoid region, was anesthetized. All sensation to cold was removed. A test tube containing ice was applied for 5 minutes. Edema in the anesthetized area resulted, but it was not so marked as in the unanesthetized area.

Experiment 9. The Prausnitz-Küstner reaction: Venous blood was taken before and 25 minutes after exposure of the hand to ice water for 5 minutes; the second blood specimen was obtained 18 minutes after the edema appeared, at the time it seemed to have reached its maximum. The serums were separated and injected intradermally into a normal person. After it had been injected and the area cooled with ice for 5 minutes, neither serum specimen caused wheal formation. Levine¹³ reported 6 positive and 5 negative results of other authors.

Experiment 10. By transferring some edema fluid from an area in which it had been produced by the application of ice to an area free from edema, Levine¹³ produced a secondary urticarial wheal. Since he had used normal saline as a vehicle to infiltrate the edema and recover the edema-producing substance, he used a normal saline injection as a control, also. We repeated this experiment and obtained similar results by injecting 0.2 cc. of edema fluid within 3 minutes, an area of urticaria 2 by 2 cm. had appeared. When 0.2 cc. of normal saline was injected, no urticaria appeared.

Doctors Westcott and Spain, of the Allergy Clinic of this hospital, investigated by the use of 87 skin tests the possibilities of a sensitivity in this patient to inhalants and foods. They were, however, unable to discover any conclusive evidence of allergy, as indicated by skin testing.

Treatment. Because of the remarkable improvement in the case reported by Bray,⁹ in which histamin hydrochlorid was used in the method of desensitization, we have instituted the same therapy. On August 5, 1935, only a few days after the patient's admission to our clinic, she received 0.1 cc. of 1 to 1000 histamin hydrochlorid intracutaneously. On alternate days she received another intracutaneous injection, each succeeding one having been increased by 0.1 cc. of the solution, until 0.5 cc. was given. Then 0.5 cc. was injected subcutaneously. This was increased by 0.1 cc. on alternate days, until 1 cc. was injected subcutaneously. This amount was tolerated physiologically but, because of the uncomfortable sensation of warmth and the marked throbbing headaches which resulted, it did not seem advisable to make further increase. The patient has, therefore, continued to receive 1 cc. of 1 to 1000 histamin hydrochlorid subcutaneously, 3 injections each week, and at the time of this report (December 16, 1935) has had 36 such injections. Objectively, the edema appears as rapidly as it did when she was first examined on July 23, 1935; at this time, however, the edema is not so severe and the time necessary for its subsidence is much less. Formerly, when her hand became edematous, when she placed it in ice water she was practically unable to move the fingers and the swelling would not subside until from 3 to 6 hours had elapsed; whereas, at this time, with the edema produced identically as before, even when it is at its maximum, she can move her fingers and almost completely close the hand. The edema entirely subsides in one hour. Symptomatically,

she no longer suffers the intense burning, the throbbing headaches and weakness that formerly accompanied the local reaction. At times, however, she still experiences mild burning accompanying the edema. Last winter she was unable to leave the house when the temperature was below freezing, whereas this year she has been able to go out in temperatures as low as 10° F. without marked symptoms. She believes that she is 60% improved.

We have not used calcium lactate as suggested by Dubbs¹¹ because we desired to determine the value of histamin alone. We intend to try it when and if the patient does not continue to improve under the present therapy.

CASE 2.—We are including, in addition, a report of a second patient whom we were unable to study in great detail but who also presents a definite clinical picture of cold sensitivity. This English woman, aged 40, is a very successful actress by occupation. She has since childhood been a strong swimmer and enjoyed especially the cold water of the British coast. In 1929, after plunging into cold water at Brighton, England, she collapsed, became unconscious and had to be taken from the water. She vomited and had a severe diarrhea. There was no generalized swelling, but innumerable "white lumps," up to 1 inch in size, appeared over her body. In 2 hours she had completely recovered, except for slight weakness. That evening she felt well but, the next day, on going into the water, the syndrome recurred. There had been no antecedent history of dietary indiscretion or any other possible exciting factors. She had no symptoms during the cold weather of the winter 1929-30, but, in the summer of 1930 when she tried swimming in cold water, the syndrome recurred. There was no further recurrence until the summer of 1934, even though she swam regularly in cold water. The symptoms returned in severe form when she tried to swim in cold water in 1934. During the winter of 1934-35, for the first time, the patient developed severe urticaria of any portion of the skin exposed to cold air. This was very disturbing, since she was often compelled to go to the theater an hour or more in advance of her performance in order that the disfigurement from the facial urticaria could subside. She also noticed that, if she took cold drinks or food such as ice cream, her lips would swell and occasionally this extended to the throat. The warm weather brought about a lessening of these symptoms but, in the summer of 1935, water less and less cold could produce collapse, unconsciousness, urticaria and the rest of the original syndrome. Finally, it was brought on when the water temperature was measured at 68° F. Physical examination revealed no significant findings. Application of ice to the surface of the forearm produced a pronounced wheal, approximately 1 square inch in area; at the same time the blood pressure of 130/75 dropped to 100/65. It is possible that this was the result of the production of "H" (histamin) substance. This test was repeated with similar results. Laboratory studies showed the following results:

Urine analysis: Clear; specific gravity, 1.016; acid reaction; no sugar or albumin; microscopic examination reveals epithelial cells.

Blood count: Red blood cells, 4,220,000; white blood cells, 4500; hemoglobin, 74%; polynuclears, 72%; small lymphocytes, 20%; large lymphocytes, 8%.

Blood Wassermann: Negative.

Chemical examination of blood: Urea nitrogen, 14 mg.; sugar, 100 mg.; uric acid, 3.9 mg. Aside from a mild secondary anemia and a slight increase of uric acid, there were no findings of importance.

Unfortunately, it was impossible to study this patient in the detail outlined in our first case report, since she had to travel with her show.

Comment. Case 1 is of interest because the experimental studies seem to give more weight to the humoral hypothesis of etiology than to any other. The blood pressure, pulse, skin temperature and gastric acidity responses of the patient to the cold urticaria are very similar to those resulting when histamin is administered. We, therefore, deduce, in agreement with other authors, that these phenomena are due to an "H," histamin-like substance liberated from the tissue cells when they are exposed to certain degrees of cold. This substance is then taken up by the blood from the edematous wheal thus formed, which results in the production of the physiological responses which simulate those of histamin. Bray⁹ states in his article, "It has been shown that histamin is liberated in the skin of normal people when the temperature of the skin is decreased to 20° F. (-6° C.)." In these cases of cold sensitivity, therefore, the threshold at which histamin is liberated is raised. In Bray's case, this threshold was raised 25° F. or from 20° F. to 45° F. Since the temperature of the skin of our patient, at which the reaction occurred, was 26.8° C. or 80.2° F., the threshold in our case is raised 60.2° F., an increase as compared with Bray's patient.

It is worthy of note that there was no evidence of allergy in Case 1 in the skin tests, in eosinophil counts, in the passive transfer of serum test (Prausnitz-Küstner reaction) or in a family and personal history. It is not clear, at present, why histamin, given as above outlined, has relieved this patient.

Case 2 is similar to cases reported by Graszl¹⁴, Tannhäuser,¹⁵ Lehner,¹⁶ Netter,¹⁷ zum Buseh¹⁸ and Affolter,¹⁹ since this case first developed symptoms and became unconscious when swimming in cold water. This patient would probably have drowned had she not been rescued. It would seem, therefore, that wider dissemination of information regarding this syndrome should be undertaken. There are undoubtedly many unrecognized cases of this condition, and the dangers to these individuals, of swimming, tub-bathing or taking showers in cold water cannot be overemphasized. It is entirely possible that the reaction could be of such severity as to produce a depression of blood pressure that would be incompatible with life.

Summary. 1. Two cases of urticaria, both females, from cold sensitivity are reported.

2. In the first case rather extensive experimental studies were possible. The beneficial effects of histamin treatment were observed.

3. That the reaction occurred at an unusually high skin temperature in this case was demonstrated.

4. Experiment points towards the humoral hypothesis of cause of reaction.

5. The second case is reported primarily because of the complete collapse when swimming in cold water.

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ESSENTIAL HYPERTENSION.

II. CONSTITUTIONAL CONSIDERATIONS.

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In the last few decades renewed efforts have been made to classify man into constitutional types and to associate certain disease-entities with one type of constitution or another. Much literature has accumulated on the subject, and a drastic divergence of opinion prevails among the various "schools" on many a cardinal topic. One has to proceed with great caution, therefore, in any study of human constitution in order to escape the temptation of biased and hasty conclusions.

With regard to essential hypertension, treatises on human constitution are conspicuous by their lack of an exhaustive independent

investigation of the matter. There are several textbook statements, however, as well as many publications in the current literature pertaining to this subject, which are at times very instructive, at others, confusing and contradictory. For instance, such an eminent pupil of DeGiovanni and Viola as Nicola Pende,¹ makes the observation that the habitus of cases of familial hypertension corresponds, among other things, to the hypergenital type. He adds that this accords well with the stimulatory action exerted upon the cardio-arterial tonus by the genital and other hormones. Yet, elsewhere in the same book, this distinguished author claims emphatically that the hypergenital or hypersthenic type of constitution is characterized by the absence of arterial hypertension. This contradiction, again, may be contrasted with the opinion of such authorities on human constitution as Julius Bauer² and Ludwig Braun³⁰ who find no characteristic habitus of any kind in cases of essential hypertension. Recently, Zipperlen³ examined a series of cases of essential hypertension, and found an overwhelming prevalence of the hypersthenic, pyknic, or apoplectic type of constitution. Barr³⁹ of St. Louis, discussing Cushing's still very debatable⁴⁰ hypothesis of pituitary basophilism in relation to hypertensive disease, expresses the opinion of many observers that the numbers of basophilic cells in the posterior pituitary lobe are greater in hypersthenic than in asthenic individuals, "thus in general tending to show predilection for the type of patient statistically most likely to have high blood pressure." Conversely, Fossier⁴ and several others^{5,6,8} depict the asthenic "tall and slender, longnecked . . . , usually emaciate" individual with the "elongated flattened chest of the paralytic type" and with the "weakness of the abdominal parietes" as the bearer of the directly opposite picture, namely, essential hypotension.⁴³ Similarly, a somewhat dimensional terminology¹⁹ describes a "linear type" with low blood pressure, and a "lateral type" with high blood pressure.

Etiologically, Fossier's conception of the narrowing of the aortic arch in hyposthenic subjects offers a purely mechanical explanation of "essential" hypotension; fetal "toxic infections," in such individuals, with endocrine (adrenal) damage and consequently⁵ lowered vascular tonus form the basis of another pathogenetic hypothesis; finally, in contradistinction to the hypertensive subjects, these "hypotensive" weaklings" are exposed as cases of constitutional mesenchymatous inferiority with a weakness of the muscular¹² and supportive tissues, exemplified by their enteroptosis, drooping shoulders, poor musculature, prominent scapulae, and flat feet. Whether or not one subscribes to this last or to any other etiological belief, at any rate one observes, for a while, some degree of harmony between the two anthropological findings: the pyknic,³¹ apoplectic, lateral, or hypersthenic¹³ individual with essential hypertension on one hand, and the asthenic, or better, hyposthenic, with essential

hypotension, on the other. This balance of views, however, is soon gravely disturbed, when such an outstanding student of blood pressure as Kylin⁷ reports cases of habitus asthenicus some of whom show a high, some others a low blood pressure. Kylin then proceeds to conclude that hypotension and hypertension are not at all syndromes of diametrically opposite nature but that they represent, instead, different phases of one and the same disorder—a conclusion which, despite Kylin's authority, should be regarded with considerable mental reservation.¹⁸ The question is rendered even more difficult by some other observations of the occurrence of essential hypotension⁸ in the hypersthenic type and of essential hypertension⁹ in asthenic and other types²³ of bodily habitus. An altogether speculative note of discord is sounded in some quarters in the form of an assertion that the constitutional factor in essential hypertension is to be conceived "not in terms of physical but of mental¹⁶ properties."

"With the idea¹² of a constitutionally increased neuromuscular tonus of the arterial system as the starting point in the study of essential hypertension," as presented in our previous publication, one might be tempted to emerge from and to abandon this swift current of gross morphologic anthropometric views because they are so divergent and because, above all, they may appear to be clinically and even theoretically entirely irrelevant. However, such an attitude may be quite erroneous. In the first place, from a general standpoint, the constitutional habitus is never an isolated coincidental phenomenon, but merely one aspect of a given constitution characterized¹¹ by a certain composition of the blood-plasma, certain chemical processes in the tissues, certain immunological reactions,¹³ certain qualities of the endocrine apparatus and of the vegetative¹⁴ system, and, clinically, stigmatized by the presence or absence of a predisposition to certain internal diseases.²⁰ In the second place, from a cardiovascular point of view, not only deviations from the normal tonus of the circulatory apparatus, especially the level¹³ of arterial²³ tension, but also many another¹¹ inadequacy²³ of the heart¹⁷ and bloodvessels are characteristically related to certain types of constitutional habitus. In this connection, one can hardly escape the thought of a possible relationship between the predominance of the asthenic habitus among the Chinese¹⁷ and the strikingly low incidence of hypertension²¹ among the same. If such views are correct, then, other things being equal, the blood pressure level of an individual may furnish a means of evaluation of the somatic constitution of that individual.¹⁵ And, *vice versa*, barring cases of nephritis, adrenal neoplasms, etc., one may be able to estimate approximately the level of arterial tension under average circumstances from the examination of the physical constitution of the given person, alone.

Faced with these problems, the objective student of essential

hypertension will do well to remain keenly interested in their final solution. If a relationship between bodily habitus and blood pressure were now clearly established, both factors, the habitus as well as its corresponding arterial tension, would most likely have to be traced to a much deeper underlying *common cause* possibly appearing early in the course of ontogenetic events. The real nature of that intrinsic cause as well as of its resultant constitutional effects would have to be understood: Are we dealing with a purely morphologic problem of *mesenchymatous* origin with one aspect in the structural elements of the arterial wall and many another manifestation in the structures responsible for the bodily habitus, *i. e.*, the architectural constitution of the whole organism? Or is it perhaps entirely a problem of "the vegetative¹² neuromuscular tonus" alone, in the arteriolar as well as in any other tissues involved, regardless of their histological origin or kinship? If the latter be the case, are these constitutional differences of tissue function actually primary, and do they solely depend upon the given autonomous²⁹ nervous system, or is the arterial tonus for example, "only secondarily under the influence of vagal²⁴ impulses" because the autonomous nervous system is ultimately "under the control of the endocrine²⁴ glands?"³⁰ (Pituitary³⁴ and midbrain.³⁶ "Pituitary basophilism," Cushing.³² Adrenals.³⁵)

Long before one can answer any of the above questions it is first imperative to find whether or not there actually exists *any* common constitutional denominator for the arteriolar tissues concerned with the maintenance of arterial tension and any other tissues of pertinent significance. The writer deems it consistent with the assumption of "a constitutionally increased neuromuscular tonus¹² of the arterial system" in cases of essential hypertension first to determine whether or not such a constitutional common denominator may be found in this very phenomenon of *tissue-tonus*, a phenomenon which Yandell Henderson²² has justly labeled "one of the most fundamental properties of life."

Deeming it wise, therefore, to refrain at present from adding statistical data on the debatable prevalence of a certain habitus in cases of essential hypertension, I propose, instead, to investigate the possible existence, to begin with, of a constitutional factor of tonus in general, and its relation to arterial tension in particular. The following is, of course, merely one approach to this question, and not a final analysis.

Assuming that essential hypertension is merely one of many clinical manifestations of a hypertonic type of constitution, then the incidence of essential hypertension in hypotonic persons, *i. e.*, in those with a diminished neuromuscular tonus, should be correspondingly low. In order to ascertain this, the blood pressure has been studied in a group of cases all of which presented a hernia acquired some time in life without injury to the site of the hernia. Such spontaneously acquired hernias are to be regarded as positive

evidence of the fact that the tensile strength of the connective tissues involved is lowered, and that the tonus of the local muscular structures is also diminished. Such³⁷ hernias show a very marked hereditary predisposition,³⁸ when repaired with utmost surgical dexterity still strongly tend to recur, and such hernias together with enteroptosis, asthenic chest-configuration, and other related findings are viewed by Tandler, J. Bauer, K. H. Bauer, and others, as signs of a hypotonic constitution. K. H. Bauer, in dealing with this constitutional type remarks, in passing, that "hypertension and arteriosclerosis in the asthenic are practically unknown."²⁸ Conversely, hernias of all types are rare if present at all in the pyknic or hypersthenic subject.⁴¹

It need not appear objectionable to attempt to study comparatively the blood pressure, *i. e.*, the expression of the arteriolar smooth muscle tonus, and the nature of the tonus of "*voluntary*" muscular elements such as we are concerned with in cases of hernia. This somewhat antiquated arbitrary division line between exclusively autonomous and exclusively "animal" innervation as applied, respectively, to smooth and striated muscle fibers, is now no longer⁴² an accepted dogma.²⁵ One need only mention the consensus of authoritative opinion expressed recently at an International Neurological Congress.²⁶ The second part of the program of that Congress was devoted entirely to the subject of muscle-tonus; a threefold tonic innervation of voluntary musculature was presented, namely, cerebrospinal, sympathetic, and parasympathetic; special emphasis was laid on the sympathetic influence upon the musculature, and experimental proof was offered of the existence and course of sympathetic nerves in the motor muscle fiber.

The possible finding of a low incidence of essential hypertension in cases of spontaneously acquired hernias might not be surprising to those who believe that the entire picture of a hypotonic constitution is the end-result of a generalized "mesenchymatous"²⁸ constitutional inferiority" with an insufficiency of all the supportive tissue including the smooth and skeletal musculature, and cardiovascular, especially arterial, hypoplasia. Furthermore, by way of contrast, such findings would be in harmony with the demonstration by Kernohan *et al.*, of the Mayo Clinic,²⁷ of arteriolar hypertrophy in cases of arterial hypertension. One may wonder, as these authors do, if the morphological picture of the arterial wall might not be the *primary* underlying factor.

Irrespective of what may be the answer to this question, we wish to find at this time whether or not the arterial neuromuscular tonus of an individual is a factor coëxistent with a similar neuromuscular tonus in this individual in tissues other than the arteries.

This investigation comprises a group of 148 cases of spontaneously acquired hernias—the majority from the New Haven Hospital and New Haven Dispensary; some are private patients of the writer. After ascertaining beyond reasonable doubt the non-traumatic

nature of the hernia in each instance, 21 cases were excluded from this study; some because of a coincidence of a disease which tends to lower the blood pressure, such as chronic tuberculosis, others because of the presence of a factor tending to raise the blood pressure, such as plumbism or nephritis. The latter was responsible for the elimination of only 2 cases, 1 a patient of 25 without any arterial hypertension, another a person of 32 with a blood pressure of 150/95. Three cases of cryptorchism on the side of the hernia (inguinal) were excluded because of a possible congenital factor in the development of the hernia. Finally, no blood pressure readings were used when taken after sedative medication had been administered to the patient.

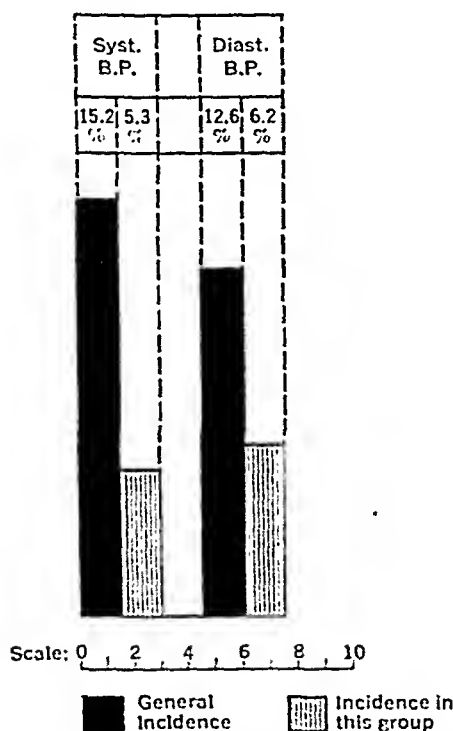


FIG. 1.—The general incidence of high blood pressure and its incidence in cases of spontaneously acquired hernias: males, all ages.

Since the incidence of hypertension in this group is being compared with the general incidence of hypertension as reported by Gager⁴⁴ in his large group of consecutive patients, the writer adopted Gager's criteria of normal blood pressure, namely, a systolic pressure of 140 before the age of 40, 150 after the age of 40, and a diastolic pressure of 90. After the elimination of the above referred to 21 cases, the remaining 127 patients were divided into 113 males and 14 females. The males only were analyzed in individual age groups conforming to the analysis of Gager. Except for the small female

group and the old age group of 60 years and over, the findings in all other cases are presented in graphic form in the accompanying three figures showing side by side the comparison of the incidence of high blood pressure in Gager's group of consecutive cases and in this group.

Fig. 1 compares the collective findings in males of all ages. It reveals a 5.3% incidence of systolic hypertension in our entire male

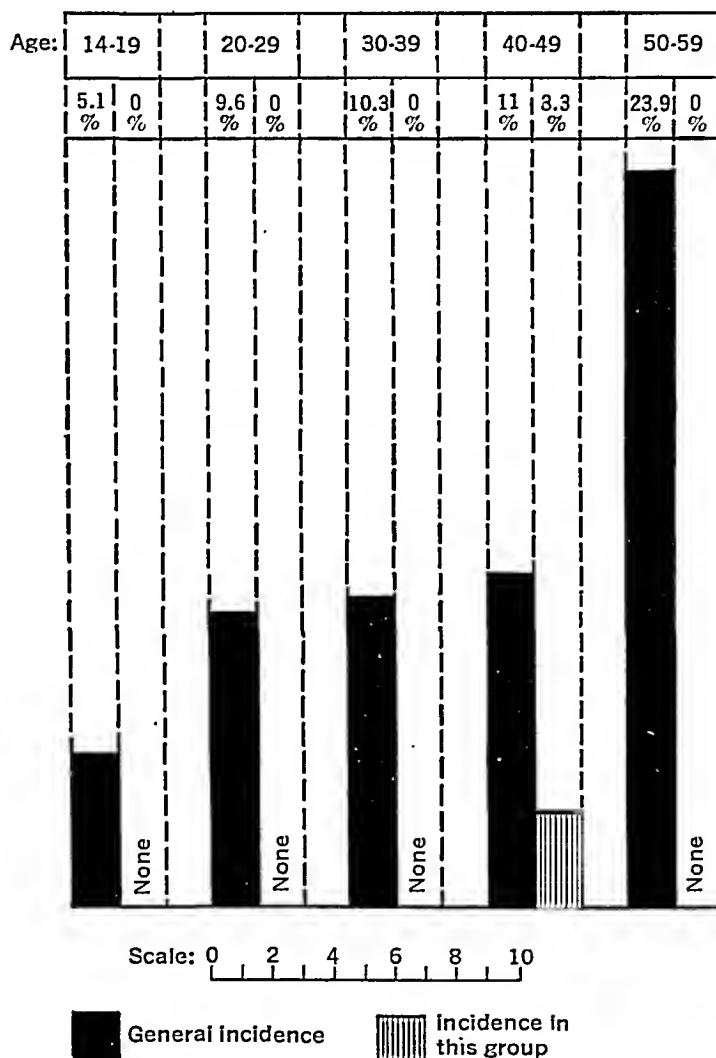


FIG. 2.—The general incidence of high blood pressure and its incidence in cases of spontaneously acquired hernias: systolic blood pressure, males.

group as compared with an expected incidence of 15.2% and a 6.2% incidence of diastolic hypertension as compared with an expected incidence of 12.6%.

Fig. 2 compares the findings of systolic hypertension in 5 individual groups of males analyzed according to age. The incidence of systolic hypertension in this series of cases in all given age groups except one is *nil* as compared with the corresponding figures of the

expected incidence of systolic⁴⁵ hypertension. The age group 40 to 49 alone shows the occurrence of some systolic hypertension, namely, 3.3% as compared with an expected incidence of 11%.

Fig. 3 shows the comparative data of the incidence of diastolic hypertension according to age. In 3 out of the 5 age groups the incidence of diastolic hypertension in our cases is *nil* as compared with the corresponding figures of the expected incidence in the same age groups. The age group 30 to 39 shows a 5% incidence of dias-

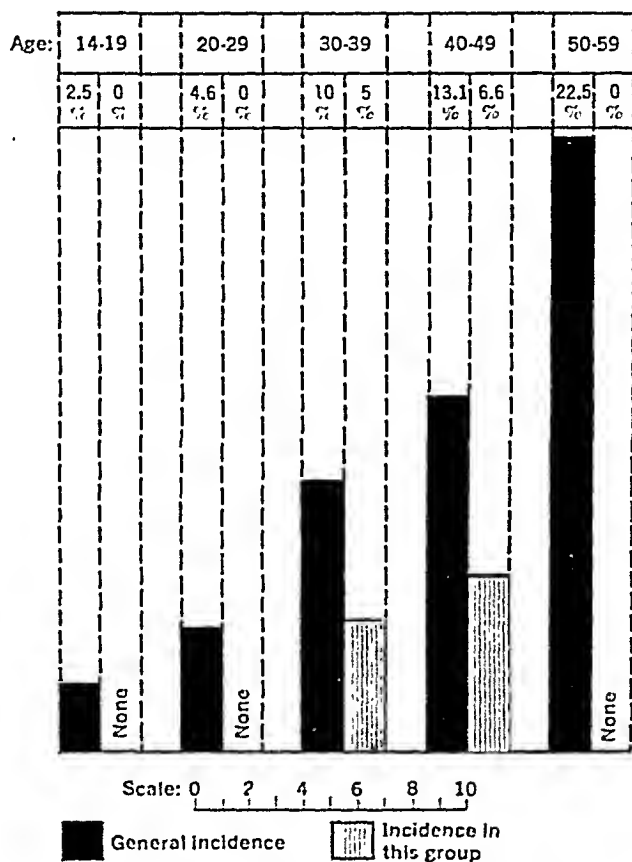


FIG. 3.—The general incidence of high blood pressure and its incidence in cases of spontaneously acquired hernias: diastolic blood pressure, males.

tolic hypertension in our cases as compared with an expected incidence of 10%. The age group 40 to 49 shows a 6.6% incidence of diastolic hypertension in our cases as compared with an expected incidence of 13.1%.

The comparative findings in the male patients of 60 and upward for which no tabular illustration is provided are as follows: In the age group 60 to 69 the incidence of systolic hypertension is 27.7% as compared with an expected incidence of 48.7%.

For the diastolic hypertension, an incidence of 16.6% in our male cases of 60 to 69 years stands out against an expected incidence of 33.7%.

In the last group of our male patients, of 70 years and over, there is an incidence of 16.6% systolic hypertension as compared with an expected incidence of 33.3%. This age group, however, is exceptional with regard to its incidence of diastolic hypertension. It is the only instance of a higher incidence in our cases than the expected incidence, the former being 16.6% and the latter 11.1%.

In our 14 female patients ranging from the age of 28 to 71 there was no instance of systolic hypertension and but 1 instance of diastolic hypertension. The latter occurred in a woman aged 71 years.

It is perhaps of some pertinent interest to note that the hernias of 35 of the patients investigated in this study were strikingly multiple, and that 4 patients had repeated recurrences some time after competent hernioplasty had been performed. These facts should not be unexpected in these individuals if their supportive tissues are constitutionally inadequate, and if they should prove to be stigmatized by a low neuromuscular tonus.

Be that as it may, the above referred to findings can be reasonably summarized in the statement that in this group of cases of spontaneously acquired hernias, the incidence of hypertension was disappearingly small as compared with the expected incidence of hypertension.

Conclusions. The number of cases studied in this investigation is limited. So is the object of this paper limited. It aims at an approach to the problem of primary hypertension from a constitutional point of view. It does not pretend to establish any new truths but to point the way in the direction of their possible existence. The writer hopes to arouse sufficient interest in this method of approach to the problem of hypertensive disease to induce others to undertake similar investigations. These should not, of course, be restricted to the finding of a strikingly low incidence of hypertension in subjects of a generalized low tissue tonus such as manifested by spontaneously acquired hernias. The possibility of a common constitutional background behind the tonus of the arteriolar musculature and the tonus of other supportive tissues in the same organism should be investigated in more than one way. The ultimate goal of such investigations is not merely to find the hereditary nature of essential hypertension or its possible prevalence in any one type of bodily habitus or in any type of constitutionally stigmatized individuals. The chief purpose of such investigations is much rather to find whether or not essential hypertension together with any other established coëxistent pertinent findings are all explicable on the basis of a certain genetically predetermined type of constitution. The specific question is: Does the strength of the original mesodermal foundation of an individual manifest itself in due time, and of inevitable necessity, in a certain strength of

tonus of the mesenchymatous derivatives including the smooth arteriolar musculature? If this be so, the generally blamed but, so far, unclarified immediately responsible blemish of increased peripheral resistance in the arteriolar bed of essentially hypertensive patients shall eventually be understood and its significance irrevocably linked with the sealed somatic fate of its bearer.

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BOOK REVIEWS AND NOTICES.

INFECTIONS OF THE URINARY TRACT. By T. E. HAMMOND, F.R.C.S., Surgeon, The Royal Infirmary, Cardiff; Consulting Urologist, The Welsh National Memorial Association. Pp. 250; 3 illustrations and 3 charts. London: H. K. Lewis & Co., Ltd., 1935. Price, 10/6.

THIS book is valuable not only to persons interested in urology but also should be of interest to the general practitioner. It takes up in a systematic way not only the infections of the urinary tract but also discusses inflammations in general. The infections of the urinary tract are discussed in an orderly fashion and include those due to colon bacillus, *Staphylococcus albus* and *aureus* and to the gonococcus. There is some mention of tuberculosis of the urinary tract but the author does not take this up to any great extent. The urinary antiseptics used are about the same as those known to us and there is some mention of ketogenic diets. The author's conception of urinary tract infections in general seems to coincide very well with our own ideas of these conditions. The book is appended with interesting discussions of (1) the bearing of the constitution upon bacterial disease, (2) some points in the nursing of bacterial disease, and (3) the practice of medicine—all of which are interesting and helpful.

F. E.

ROENTGENOGRAPHIC TECHNIQUE. By DARMON ARTELLE RHINEHART, A.M., M.D., F.A.C.R., Professor of Roentgenology and Applied Anatomy, School of Medicine, University of Arkansas; Roentgenologist to St. Vincent's Infirmary, Baptist State Hospital, Missouri Pacific Hospital and the Arkansas Children's Hospital, Little Rock, Arkansas. Pp. 431; 183 illustrations. Second Edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$5.50.

TIME has already established the usefulness of this textbook. While the general plan of the book is similar to the first edition, its value is enhanced by the edition of many recent advances in radiology. The first 12 of its 21 chapters contain discussions of Roentgen ray machines, the nature and properties of Roentgen rays, dark room technique, exposure combinations and various other physical factors concerned with applied radiologic physics. The rest of the book describes most of the roentgen examinations used by radiologists today. The verbal descriptions are excellently illustrated by photographs of patients in position for examination with roentgenograms obtained of each technique.

E. P.

THE HARVEY LECTURES, SERIES XXX. By DOCTORS WILLIAM BOSWORTH CASTLE, WILLIAM CUMMING ROSE, WILBUR A. SAWYER, ALFRED N. RICHARDS, E. C. DODDS, G. V. ANREP, FRANCIS G. BLAKE, and JOHN H. NORTHROP. Delivered under the Auspices of the Harvey Society of New York, 1934-1935. Under the Patronage of the New York Academy of Medicine. Pp. 270; illustrated. Baltimore: The Williams & Wilkins Company, 1936. Price, \$4.00.

THE latest volume of this well known series presents 8 lectures, all by well known authorities in their special fields. The wide range that is covered is readily shown by the list of lectures and their subjects: "The Etiology of

Pernicious and Related Macrocytic Anemias," by William B. Castle, of Harvard; "The Significance of the Amino Acids in Nutrition," by William C. Rose, University of Illinois; "The Present Geographic Distribution of Yellow Fever and its Significance," by Wilbur A. Sawyer, The Rockefeller Foundation; "Processes of Urine Formation in the Amphibian Kidney," by A. N. Richards, University of Pennsylvania; "Specificity in Relation to Hormone and Other Biological Reactions," by E. C. Dodds, The Middlesex Hospital, London; "The Relation of the Circulation in Voluntary and Plain Muscle to Activity," by G. V. Anrep, Egyptian University; "Pneumothorax in the Treatment of Pneumonia," by Francis G. Blake, Yale University; "The Isolation and Properties of Crystalline Pepsin and Trypsin," by John H. Northrop, The Rockefeller Institute. Adverse criticism does not occur to the Reviewer and praise seems superfluous. E. K.

ABORTION. Spontaneous and Induced. Medical and Social Aspects. (This volume is one of a series dealing with medical aspects of human fertility sponsored by The National Committee on Maternal Health, Inc.) By FREDERICK J. TAUSSIG, M.D., F.A.C.S., Professor of Clinical Obstetrics and Clinical Gynecology, Washington University School of Medicine, St. Louis. Pp. 536; 146 illustrations, and 27 tables. St. Louis: The C. V. Mosby Company, 1936. Price, \$7.50.

THE extreme importance of abortion as a medical and social problem of the present time justifies the appearance of this very comprehensive monograph upon the subject. The conservative figures offered for the United States refer to 681,600 abortions annually, with a death toll of \$179. These data are believed to be minimal. The socio-medical aspects may be briefly summarized in the known fact that one of every four puerperal deaths follows an abortion.

A wide review of the world's literature for years back is utilized to form a historical and factual background upon which the author has developed his picture of the present day situation, with its clinical, pathologic, legal and social aspects.

Of interest from a standpoint of comparative obstetrics is the chapter by Dr. W. L. Williams of Cornell University on abortion in animals. Suggestive, at least, is the discussion of trichomonas as a possible cause of abortion in animals.

The chapter on prevention details the various measures which may be used either before or during pregnancy or to prevent uterine contractions. Taussig is skeptical as to the value of hormone therapy in prevention. Very important is the chapter on treatment, displaying a frankly conservative attitude toward febrile abortions.

The indications for therapeutic abortion, a chapter twice as long as any other in the book, carries one widely afield as the author reviews the reasons found in the literature for the interruption of pregnancy. In the discussion he follows Winter's outline. The relation of sterilization to this procedure is discussed. The attitude of Russia toward legalized abortion is discussed in a separate chapter, although the reaction of other European countries is interestingly mentioned here. Although misquotation of portions of this chapter occurred in a recent lay journal review of this book, one feels in reading the closing sections of this chapter that the author is quite broad-minded toward a widening of the socio-economic indications for therapeutic abortion.

The legal and medico-legal aspects of abortion are fully considered. The laws of the states and countries are annotated and the medico-legal aspects of abortion provide words of wisdom and caution for the practitioner.

This most able presentation of one of our most serious and common problems deserves to be widely read, and the book belongs on the work shelf of every obstetrician.

P. W.

NEW BOOKS.

Disinfection and Sterilization. By ERNEST C. McCULLOCH, M.A., D.V.M., PH.D., Biological Research, Pennsylvania Salt Manufacturing Company, etc. Pp. 525; 53 illustrations, 232 tables. Philadelphia: Lea & Febiger, 1936. Price, \$5.50.

The Patient and the Weather. Vol. 1, Part 2, Autonomic Integration. By WILLIAM F. PETERSEN, M.D., with the assistance of MARGARET E. MILLIKEN, S.M. Pp. 781, lithographed; 366 illustrations. Ann Arbor: Edwards Brothers, Inc., 1936. Price, \$9.00.

Frigidity in Women. Its Characteristics and Treatment. By DR. EDWARD HITSCHMANN and DR. EDMUND BERGLER, Director and Assistant Director, respectively, of the Psychoanalytic Clinic in Vienna. Authorized translation by POLLY LEEDS WEIL, of New York. Pp. 76. Washington: Nervous and Mental Disease Publishing Company, 1936. Price, \$2.00.

Marconiterapia. Trattato sulle Onde Corte. Nella Biologia e nelle Applicazioni Terapeutiche. By PROF. PIETRO CIGNOLINI, Capo del Reparto Radiologico ed Aiuto volontario dell'Istituto di Clinica Medica Generale della R. Università di Genova. In collaboration with PROF. F. BARATTA, ING. A. ASCIONE and DOTT. C. BIANCHI. Preface by PROF. GIUSEPPE SABATINI, Direttore della Clinica Medica Generale della R. Università di Genova. Pp. 362; 152 illustrations and 12 tables. Milan: Ulrico Hoepli, 1936. Price, Lire, 50.

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PROGRESS OF MEDICAL SCIENCE

PATHOLOGY AND BACTERIOLOGY

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RECENT WORK ON THE TISSUE CHANGES IN VITAMIN "A" DEFICIENCY.

MANY reports have been published on the tissue changes which are found in animals that have been fed diets deficient in vitamin A. Only a comparatively small number of the more recent and more important papers will be discussed in this review.

Since 1922, when McCollum and his associates¹ separated the two vitamins in cod liver oil, vitamin A has been known to be essential for growth in young animals, and many investigators have even assigned to it a special growth promoting effect. For example, Sampson, Denison and Korenehevsky,² in a series of painstaking experiments, showed that young rats deprived of vitamin A excreted somewhat more N, and grew much less per gram of food eaten than did litter mates fed the same amount of the corresponding adequate diet. The experiments were terminated when the avitaminotic rats showed the sudden drop in food consumption which usually precedes the last week of life. In other words, they showed that the metabolic rate was increased to some extent in vitamin A deficiency. Braman and his collaborators³ obtained the same general results in similar experiments, although in this case all the rats were first depleted of vitamin A before they were fed the complete or the nearly vitamin A free diet. The differences in weight gain were less marked under these conditions than in Sampson's experiments. Recently Chevallier and Baert,⁴ studying the metabolic rates in normal and vitamin A deficient rats, found that in the latter it was increased about 13%. However, this increase would not be sufficient to explain more than a small part of the decreased body weight.

Orr and Richards⁵ have recently challenged the statement that vita-

min A is preëminently growth-promoting. They admit, of course, that as an essential food factor it has an effect on growth. These workers demonstrated definite growth in length of the leg bones during the period when the rat was losing weight on an A free diet, and suggest that the loss in weight is due to pathological changes, especially in the gastro-intestinal system. Even after 3 or 4 weeks on the diet, such lesions were seen in 75% of the animals and they suggest that microscopic lesions might be present a week or so earlier, at the time when the weight curves of the deficient animals begin to fall below those of the controls. That earlier lesions are likely is supported by Mouriquand's experiments,⁶ where, by means of a special light and a corneal microscope, he demonstrated ulceration of the cornea in animals that had been fed the A deficient diet for only 18 days—fully 3 weeks before the development of gross xerophthalmia. At the present time the question of a specific growth promoting effect of vitamin A is not settled.

The effect of the lack of this factor on the endocrine organs has also not yet been solved. In their classical experiments, Wolbach and Howe⁷ (1925) stated that the pancreas, thymus, thyroid, pituitary and testes showed atrophy as compared with the glands of adequately fed controls. The parathyroids and adrenals showed no decided decrease in size. All the rats were fed only 5 gm. a day, which is less than they would ordinarily consume. Korenehevsky⁸ was unable to confirm these findings when he compared the organ weights per 200 gm. of body weight in A deficient rats, and in controls fed the same amounts of a complete diet. The testes in the deficient animals were heavier, but histologically they showed edema and degeneration. The prostates and seminal vesicles were also heavier in the A deficient animals. No change in percentage weight was noted in the adrenals, thyroid, hypophysis and thymus. De Ruyter⁹ has recently stated that the thyroid shows atrophy in severe vitamin A deficiency, and that there is also involution of the thymus. Vitamin A therapy corrected these changes. The changes in the thymus may be connected with the decreased rate of growth. Coplan and Sampson¹⁰ have recently studied the effect of a deficiency of vitamin A on the thyroid gland of rats. In the males they found the thyroids consistently smaller in the avitaminotic rats than in the controls. The converse held true for the females, although these all died within 37 days. On section, they found early a hyperplasia of the epithelial cells, which became high and dome shaped and looked similar to those seen in rats fed iodine deficient diets. Later the epithelium degenerated and this seemed to be specifically caused by a lack of vitamin A. They suggest that the A deficiency at first alters the metabolism of the thyroid epithelial cells, so that iodine is not normally absorbed or utilized and this causes a relative deficiency of iodine with the consequent thyroid hyperplasia. Lockwood and Hartman¹¹ found the adrenals atrophied in vitamin A deficient rats as compared with normal controls when calculated as per cent of body weight. Blumenfeld¹² also found atrophy of the adrenals, chiefly of the cortex, unless marked infections were present when hypertrophy supervened. Vogt¹³ found that the pituitary of healthy men up to 50 years contained a constant quantity of vitamin A. After 60 years the vitamin content was less, and the slow growth of tumors in such individuals may be due to this cause. The

relation of vitamin A to the growth hormone was not solved. Nothing as yet suggests that overfunction of the thyroid explains the increased basal metabolism. Mason and Wolfe¹⁴ were unable to demonstrate any definite abnormality in the endocrine activity of the ovary or pituitary in vitamin A deficiency.

Metaplasia of Epithelial Tissue. Wollbach and Howe,⁷ in their excellent experiments which were reported in 1925, demonstrated that striking structural changes occurred in the epithelia of the nose and upper respiratory tract, the ducts and acini of the salivary glands and pancreas, the ureters, pelvis of the kidney, the bladder, many of the genital organs, the cornea and the paraocular glands of rats fed diets lacking vitamins A and D. The epithelium of the seminiferous tubules and the kidney tubules did not show this metaplasia. According to Mendel,¹⁵ metaplasia of the trachea and bronchi is not common and usually only atrophy of the lining cells is found. In general, it has been regularly found that various types of epithelium, of entodermal, mesodermal or ectodermal origin showed the same morphologic changes. Atrophy of the cytoplasm of the original epithelial cells, which may be so slight as to necessitate comparison with normal cells to show it up, always preceded the later changes and possibly stimulated them. Then small nests of deeper staining epithelial cells appeared at intervals in the basal layer. These grew in all directions either as clumps or sheets and spread out underneath the original epithelium which retained its viability until it was entirely undermined. The old epithelium was sloughed off and the new squamous epithelial cells multiplied rapidly and in the upper layers showed keratinization. Some later workers found that the metaplasia varied from isolated nests to complete transformation. It has also been suggested that the decreased secretion of the associated glands promotes desquamative changes. Ducts of glands, small bronchi, or ureters may be blocked by the keratinized cells that are being formed and sloughed off with the resultant formation of cysts or abscesses. Wollbach and Howe⁷ found considerably fewer epithelial infections in their rats than did Goldblatt and Benischek¹⁶ or Green and Mellanby.¹⁷ The infections are usually caused by bacteria which normally are present at the sites involved, and their development is favored by the poor drainage, the dead tissue and the lack of ciliary action and mucus secretion which are the sequels of the metaplasia. Goldblatt and Benischek confirmed Wollbach's work and showed that similar changes were caused by a diet deficient only in vitamin A. Seifried¹⁸ studied the tissue changes in the chicken in great detail and found them to be essentially the same as those in the rat.

It is thought that the blood supply of the skin epithelium is poor,¹⁹ which would probably mean a low concentration thereof of vitamin A, and the absence of this vitamin has been found to stimulate cell multiplication (*i. e.*, in new growths).²⁰ This may explain the constant normal growth of the epidermis. When vitamin A is deficient in the diet, all the epithelial tissues would be low in this factor, and this lack, following the stimulation of the original atrophy of the normal epithelium, may give rise to the multiplication and later keratinization of the squamous cells. This typical transformation of epithelial cells in many localities of the body, commonly known as metaplasia, has been found to occur in many different species of animals when vitamin A

free diets are fed. For example, human beings,²¹ monkeys,²² mice,²³ rats,⁷ guinea pigs,²⁴ chickens,¹⁸ rabbits,^{22b} all respond in this way. Swine²⁵ and cows²⁶ also show similar gross pathologic changes. In a great many cases only a few of the many possible sites show metaplasia, and in a group of animals of the same species, age, sex and litter considerable variation is commonly seen in the order and number of the organs involved and in the extent of the metaplasia.

In a good many experiments only the gross lesions, such as abscesses, have been recorded. Whether or not an abscess occurred would probably depend to some extent on the type of bacteria which happened to be present at the site of the metaplasia. Chance variations in the number and variety of the bacteria may explain some of the variations found. Also it is possible that the vitamin A storage due to previous feeding varies and that animals vary in their ability to absorb and utilize this vitamin. Considerable variations are also found when we compare the results of vitamin A free diets in various species of animals. For example, the mouse does not show metaplastic changes in the salivary gland at the base of the tongue, whereas cysts or abscesses at this site are very common in the rat; the pig does not develop xerophthalmia, whereas the rat frequently does so.

Lesions in the Nervous System. As early as 1914 Hart and McCollum^{27a} noted that pigs kept on diets of wheat and salt mixtures developed striking incoördination which could be cured if butter was fed. These same workers 2 years later^{27b} fed pigs a diet largely whole wheat and containing little vitamin A, and found that after about 9 months the animals developed incoördination of the muscles and even blindness. Sections of the spinal cord showed shrunken motor nerve cells, apparently compressed by fluid about them. The processes were partly degenerated, the nuclei shrunken and the Nissl granules crowded together. The addition of either meat scraps or alfalfa, *i. e.*, mainly protein, or vitamin A, with some mineral salts as well, prevented the onset of the disease, which was thought to be due to the toxicity of the whole wheat. The same symptoms also occurred in dogs.²⁸

In 1926 Mellanby²⁹ noted that dogs fed a diet deficient in the fat soluble vitamins and rich in cereals developed symptoms attributable to nerve lesions. Degenerated nerve tracts in the spinal cord were demonstrated in these animals. Since 1929 several investigations on this question have been carried out.

Hughes and his collaborators³⁰ found that pigs fed vitamin A deficient diets did not develop xerophthalmia, although some had watering of the eyes and slight swelling of the eyelids. They regularly after 6 months or more showed incoördination, spasms and blindness, apparently of nervous origin. Hearing and smell seemed also to be impaired. By the Marchi method they found definite annular degeneration of nerve fibers in the optic thalamus, optic, femoral and sciatic nerves, and in certain parts of the spinal cord. These nervous symptoms could be prevented or cured by adding various sources of vitamin A to the diet.

E. Mellanby has investigated this problem extensively, and has published a series of papers.³¹ His diets contain large amounts of cereals and no vitamin A. The nervous manifestations were not invariably produced unless some apparently toxic substance such as wheat germ or ergot was added as well. The addition of vitamin A would prevent

the symptoms and also cure them promptly if they were of short duration. Lesions of long standing were, however, beyond repair. Young dogs, rabbits and rats were used. The symptoms included incoordination, paralysis, abnormal head movements and probably deafness.

Degenerative changes were found in the myelin sheaths of the nerve fibers in the spinal cord, and there was more degeneration in the cervical than in the lumbar region. The anterior columns (which contain sensory tracts in the dog), the anterolateral, the lateral posterior column (Burdach's) and the direct cerebellar tracts were commonly involved. In other words, the sensory columns seemed to be particularly picked out. The degeneration was seen in fibers scattered about in the tracts and not in groups of fibers lying together. The crossed pyramidal tracts were usually, but not always, free from degeneration and a few descending tracts which were associated with the midbrain or medulla suffered. The changes were not accompanied by cell invasion or other evidence of inflammatory reaction. If the nervous symptoms were allowed to continue for some time the fibers ultimately disappeared.

The peripheral nerves also showed degeneration. Although not entirely confined to afferent peripheral nerves, these showed the more intense degenerative changes (demyelination) and this applied both to the afferent spinal nerves and to other sensory nerves (optic, vestibular and cochlear of VIII, and sensory division of trigeminal).

In a rabbit showing early xerophthalmia, a few degenerated fibers were found in the first division of the trigeminal which supplies sensory fibers to the surface of the cornea. In more severe xerophthalmia, more advanced nerve lesions were found. If xerophthalmia was present in one eye but not in the other, sometimes some degeneration was found in the nerve supplying the normal cornea and sometimes it was not. Mellanby suggests that possibly the nerve and epithelial changes arise synchronously and that the generalized epithelial metaplasia is the result of the involvement of the afferent nerves throughout the body. In the early stages the myelin droplets did not invade the axis cylinders, but appeared as rings when stained with osmic acid. The whole nerve fibers were swollen. In more advanced cases many fibers were found in which degenerated myelin occupied the positions of the original axis cylinders. The degenerative changes affected only the first two neurones of the afferent nerves.

The motor cranial nerves escaped, although occasionally some degeneration was found in the third. If the nutritional disturbance had been very prolonged, some of the anterior nerve roots showed degeneration. As yet no degeneration has been found in the vagus nerve, even in its afferent fibers.

Degenerative changes were also seen in the nerve cells, including those of the dorsal roots, the Gasserian ganglion, Clarke's column, the Purkinje cells and the vestibular nucleus. It is seen here also that it is the afferent side that suffers most, although in the midbrain, the red and the oculomotor nucleus, and the dentate nucleus in the cerebellum sometimes suffer some changes.

M. Mellanby³¹ demonstrated marked thickening and irregular downgrowths of the epithelium about the gingival margins, widening of the sulci and frequent pyorrheal infections in dogs fed vitamin A free

diets. Recently M. Mellanby and King³² have demonstrated degenerative changes in the fibers of the sensory nerves which supply these sites, and also in nerve cells in the Gasserian ganglion.

It is quite possible that the primary lesions are in the nerve cells and that the fiber changes are secondary. The changes in the nerve cells are unfortunately very variable. The Nissl granules may appear powdery, may be clumped around the nucleus or the periphery or may be absent. The nucleus may be swollen, shrunken, eccentrically placed or absent. Even in the animals fed the adequate diet a few of the nerve cells are abnormal, but Mellanby assures us that the changes in the animals fed the diet deficient in vitamin A are much more marked and widespread. As yet there is no suggestion why the sensory nerve cells are injured and the motor nerve cells largely spared. Also, are we to suppose that the primary atrophy of the original epithelium which Wolbach and Howe emphasize, and also the initiation of the squamous differentiation of the basal cells are due to changes in the trophic nerves? It is possible that the squamous cells of the normal skin are poorly supplied with nerve fibers, and this type of differentiation may follow when there is a lack of nerve impulses to restrain the multiplication of the epithelial cells, such as might occur in areas innervated by such partially degenerated nerves.

Zimmerman³³ and Aberle³⁴ observed similar clinical signs in rats fed a vitamin A free diet containing cornstarch, but no cereals. They found myelin degeneration in the sensory tracts on the periphery of the cord in all their animals, but the posterior columns were involved in only about one-half of them. The medullary sheaths of the brachial plexuses and sciatic nerves always showed degeneration, but in addition 4 of 8 animals examined showed degeneration of the vagus. As a result of their staining methods, they concluded that the changes in the peripheral nerves were of longer duration than those in the cord. They occasionally found changes in the motor tracts and the anterior roots. They suggested that lesions in the cord followed those in the peripheral nerves on the sensory side and produced those in the peripheral nerves on the motor side. Animals which were fed the deficient diet for 5 weeks, but which showed no nervous signs, had normal nerves, but one rat which showed no clinical symptoms after 58 days on the diet had extensive peripheral myelin degeneration. The authors suggest that possibly it would have developed symptoms soon. Animals which were killed 4 days after they had been cured of their nerve symptoms by 20 days' treatment with cod liver oil, still showed moderate degeneration of the peripheral nerves and pyramidal tract. Possibly if a longer interval had elapsed between the cure and the examination more improvement would have been seen in the nerves. These authors also demonstrated that partial starvation but with adequate rations of vitamins did not cause lesions of this nature.

Sutton, Setterfield and Kraus³⁵ introduced two new methods into the study. Their rats were fed the A deficient diet until they stopped increasing in weight (60% showed incipient ophthalmia) and were then given about 30 mg. of butter daily. If no vitamin A (butter) was given they became so weak and emaciated that the nerve changes could not be properly observed. After about 2 weeks on this low A diet they showed incoordination of their back legs, and gradually they became

unable to use them. These authors found the Marchi process unsatisfactory and used instead a method in which the nerves were cut in frozen sections and examined with a polarizing microscope. Normal myelin consists mostly of cerebrosids, phosphatids and sulphatids which rotate the plane of polarized light (anisotropic) and is almost entirely free from true fats. When myelin degenerates it changes from a mixture of these substances to true fats (triglycerids) which do not rotate the polarized light (isotropic). Prior to the onset of ophthalmia, swelling of the axis cylinders and nerve fibers and some irregularity of the myelin was seen. Later, vesicular areas of isotropic degeneration appeared in the myelin. The number of fibers involved increased with the length of time the animals were kept on the partially deficient diet. If the animals were fed the same diet with supplements of carotene from weaning, the nerves showed no changes. These authors also suggest that the early degenerative changes in the nerves may be responsible for the epithelial metaplasia. The animals at no time showed spasms or convulsions, possibly because their diet contained no cereals. Some other authors claim that the accuracy of this method for showing myelin degeneration has not been established.

Seifried³⁶ made a study of the nerve lesions occurring in hens fed vitamin A free diets. Clinically the birds showed ataxia, incoördination, drowsiness and convulsions. The changes in the spinal cord fibers resembled those found by the other investigators, but in addition the anterior horn cells showed definite degenerative changes. Degenerative changes in the myelin sheaths in the sciatic, brachial and optic nerves were observed. In the brain a variety of very definite pathologic changes as observed in the ganglion cells of the motor cortex, of the nucleus dentatus, of the nuclei of the medulla oblongata, and more seldom in the Purkinje cells of the cerebellum. In other words, more changes were found in the motor nerve cells by Seifried than by the other investigators.

John³⁷ found the sensibility of the cornea in advanced stages of vitamin A deficiency in man to be markedly reduced, whereas conjunctival sensibility was much less reduced. He believes these findings are evidence of a central nervous system lesion. Bloch also stated that children suffering from xerophthalmia were very indolent in the first stages and later extremely irritable.

Suzman and his collaborators³⁸ tried without success to produce nerve lesions in adult dogs by feeding a diet devoid of vitamin A. These authors suggest that their dogs died of some other unknown deficiency before the nervous signs of vitamin A deficiency developed.

Grinker and Kandel³⁹ found that 4 monkeys fed an A deficient diet of poor quality (polished rice and aerated butter) showed neither nervous symptoms nor degenerative lesions postmortem. It was not stated whether the monkeys were adults. Weil³⁹ reported that 8 young rats fed on a synthetic A free diet did not show any marked weakness of their hind legs or any changes in their nervous systems. Davison³⁹ also was unable to confirm Mellanby's findings in rats fed similar diets. Neither of the last two authors have reported their findings in detail.

Hale⁴⁰ described in 1933 3 litters of pigs farrowed by sows on a vitamin A deficient ration which were without eyes or blind.

Night Blindness. Mellanby⁴¹ found that the retina of a rabbit fed a diet deficient in vitamin A for 4 months was much thinner than that of the control rabbit. In the bipolar and ganglion layers particularly there were fewer cells which stained less intensely. The nuclei were eccentric and the Nissl granules powdery in the ganglion cells. In a dog that had been fed a similar diet for over 7 years the whole ganglion cell layer in the retina had disappeared and the optic nerve had been replaced by connective-tissue strands.

Wald^{42a} has recently demonstrated by spectrographic methods that vitamin A is present in the retina, pigment epithelia and choroid layers of frogs, pigs, sheep and cattle. This same worker^{42b} has also shown that the retinas of frogs that have been kept in darkness for 16 hours (dark adapted) contain visual purple but only a trace of vitamin A. Visual purple when treated with chloroform yields a new carotenoid, retinene, which is probably combined with a colloidal protein to form visual purple. Light-adapted frog retinas on the other hand contain vitamin A but no retinene. In an eye in which the retina and inner layers are intact, visual purple is regenerated from vitamin A. Some vitamin A is lost in the eye and for normal vision must be made good from the diet. Vitamin A, according to this author, is "a simple though special component" in the visual purple cycle.

Skin. Very few investigators have described changes in the skin and epidermal structures of animals fed vitamin A free rations. Steenboek and his collaborators,⁴³ however, in 1922 found that in rats, especially if they were over 4 months of age, the hair became thin and bushy, growths appeared on the skin of the ears, tail and nose, and eventually sores developed on the body and legs which healed with difficulty. Possibly these growths on the ears and tail were due to mites as these are prone to occur in such animals.⁴⁴ None of these changes would appear to be specifically caused by a deficiency of this vitamin. Manville⁴⁵ found that such animals showed decreased activity of the sebaceous glands, with dry bristling hair that readily fell out. Gudjónsson⁴⁶ noted also that the fur lost its smoothness and that the feet became scaly and rough. Klemola⁴⁷ has described a keratoplastic reaction in hoof formation in the horse, also due to a lack of vitamin A.

In 1883 De Gouvêa⁴⁸ stated that keratomalacia was associated with a dry, scurfy-looking skin which was less sensitive than normal and that the hair fell out. Such findings have frequently been reported since.^{49a} For example, Bloch^{49b} observed that infants suffering from this eye condition had dry, scaly, shrivelled skins. Occasionally bleaching of the hair has been noted also.⁵⁰

In their report of an autopsy on a 5-months-old infant that died with keratomalacia, Wilson and Du Bois⁵¹ noted that the skin had a peculiar waxy feel and that there was slight desquamation on the abdomen.

Recently, Pillat⁵² and Frazier and Inn⁵³ have reported two series of cases of keratomalacia associated usually with skin changes. The patients were adult Chinese and the skin lesions usually preceded those in the eyes. Both authors noted that the skin was dry and covered either with fine branny or larger scales of horny epithelium. In some cases the skin was darker than normal and took on a dull slate color. There were many comedones on the face and the hair was dry and lusterless. None of the patients showed signs of scurvy, beri-beri or pellagra.

The diet included white cabbage and salted vegetables and the former would provide enough vitamin C to rule out the possibility of scurvy. Pillat's patients suffered from multiple painless skin infections which cleared up rapidly with a high vitamin A diet. Frazier and Hu noted that the skin appeared finely wrinkled in places. The most striking finding in these patients was an eruption of usually raised papules (spinous, according to these authors) at the sites of the hair follicles on the extensor surfaces of the upper and lower limbs, the lower abdomen, the chest and the buttocks. The papules were usually deeply pigmented. Microscopically, they found that the epidermis around the papules was moderately hypertrophied, although later authors have described it as markedly hypertrophied. The mouth of the follicle was plugged by a dense mass of cornified material, laid down in more or less concentric laminæ—which one would expect was the product of metaplastic cells lining the follicle. The plugs either projected beyond the surface of the skin or were flush with it. The lower part of the follicle was atrophied and sometimes cystic and there was an increase in the intracellular pigment in the surrounding epidermal cells. Considerable numbers of lymphocytes, fibroblasts and occasional endothelial cells were found in the reticular tissue around the follicle. Only a few remnants of sebaceous glands were seen in the midst of the inflammatory zone. The ducts of the sweat glands were dilated and occluded by keratinized material, and the epithelial cells of the tubules were shrunken and irregular. The lumen of the glands was dilated. Pus-tulation occurred in about one-third of the cases. The infection apparently started in the plugs and spread into the perifollicular tissue. Ulcers were sometimes seen in the lining tissues of the distended follicles. No local treatment was used, but after 2 weeks of a high vitamin A diet the skin was definitely moister. The ulcerative lesions healed promptly. The papules decreased in size slowly and finally disappeared, leaving delicate atrophic pigmented scars. The cases were followed at the most for only 2 months and the skin had not become normal within that time. These findings fit in so perfectly with those seen elsewhere in vitamin A deficiency that it is hard not to believe them specific. Wiltshire,⁵⁴ however, described very similar lesions in cases of latent and manifest scurvy amongst Serbian troops.

In 1933 Loewenthal⁵⁵ described an almost similar condition among East African prisoners. The papular eruption was present in all cases of xerophthalmia and night blindness. It occurred chiefly on the extensor surface of the arms and outer and front surfaces of the thighs. This author noted that the dryness of the skin did not include that of the face or scalp. Itching was common. He gave 1 ounce of cod liver oil daily, leaving the rest of the diet unchanged, and no local treatment was applied. All of the night blindness and xerophthalmia and 98.6% of the dermal lesions were cured after 9 weeks of this treatment.

Nieholls of Ceylon⁵⁶ reported the same general findings and called the condition phrynoderma (toad skin), after the native name. Two-thirds of the patients who were suffering from this affliction had eye symptoms such as dimness of eyesight. Keratomalacia was only found in one-eighth of these patients. In the later stages they frequently developed neuritis and diarrhea and some deaths resulted.

Goodwin⁵⁷ has recently reported a case with a similar eruption in a 10-year-old child in England. It was associated with a smooth red tongue and apparently pyorrhea. On a high vitamin A diet plus 4 drachms of cod liver oil daily, the dryness of the skin, the eruption, and the yellowness of the conjunctiva disappeared, the tongue papillæ regenerated and the gums improved in from 3 to 6 weeks.

Sweet and K'Ang⁵⁸ from China have recently described 16 cases of keratomalacia. Only some of them showed the typical papules described above and the incidence was therefore considerably lower than in the other series, but most of these patients were very young.

Nicholls⁵⁹ also described a condition of "sore mouth" in which the patient showed patches of superficial erosion in the mucous membrane of the lower lip or tongue and later a red glazed tongue. It was only about one-quarter as common as phrynoderma. About 80% of the sore mouth patients showed phrynoderma as well. Glazed tongues have been described in rats fed diets deficient in the vitamin B complex. In deficiency diseases in man, usually several food factors are lacking and the resulting pathologic picture is very complicated. Nicholls stated that the Cingalese diet was very short in fat soluble vitamins and probably also in vitamin B₂.

MaeKay⁶⁰ has reported some interesting results with English infants, half of whom were fed milk and solid food, and the other half the same diet plus extra vitamin A (a concentrate made from mammalian livers). The latter group showed a considerably lower incidence of skin infections, such as sore buttocks, intertrigo, and dribbling rashes. No obvious change in skin texture preceded this. No alteration was noted in general resistance or growth.

Several authors have found skin infections of various kinds: furunculosis, pyoderma, ulcers^{49, 61} and so forth, usually common among individuals suffering from vitamin A deficiency. For example, Spence⁶² found that two-thirds of his 17 patients with night blindness and xerophthalmia suffered from persistent skin infections which cleared up rapidly, as did also the eye symptoms, when an adequate diet including cod liver oil was fed. Bloch⁶³ found severe infections, including pyoderma, common in his xerophthalmic children. For further references to such cases see MaeKay's excellent review.⁶⁴

Stomach and Intestines. In their early work (1925) Wolbach and Howe⁷ stated that no metaplastic changes were found in the stomachs and small or large intestines of vitamin A deficient rats. Later (1933)⁶⁵ these authors found that the forestomach of such rats, which is normally covered with squamous epithelium, shows focal hyperkeratosis. Several other investigators, including Fujimaki, Fridericia, and Moll and his collaborators,⁶⁶ have reported similar findings. Fujimaki stated that the hyperkeratosis and papillomata were more marked if the diet contained considerable fat. When exclusive fat diets, even containing considerable amounts of cod liver oil, were fed, similar changes were observed. However, such a diet is so deficient in many other food factors that the results are of questionable value. Fridericia examined by laparotomy the stomachs of a series of rats that had been fed a vitamin A free diet intermittently for 18 weeks. They showed papillomata. They were then fed a normal diet for a year. At the end of that time the papillomata had disappeared in 19 of the 21 rats. The

epithelial overgrowths seem therefore to be definitely due to this specific deficiency. Moll *et al.* found the flat epithelium was hypertrophied and surrounded for the most part in ring form an atrophied or still relatively normal part of the epithelium. The changes were most frequently found at the margin of the squamous and glandular epithelium where the processes first appeared to be atrophic and degenerative, but later became hypertrophic, apparently as the result of infection. In a large series of vitamin A deficient animals, Arons and van der Rijst⁶⁷ found 64% had changes similar to ulcers in the squamous epithelium of their stomachs, which these authors thought were probably non-specific. Pappenheimer and Larimore⁶⁸ had previously stated that similar gastric lesions were possibly due to the swallowing of hair. Manville⁶⁹ found that white rats on a vitamin A deficient diet developed gastric ulcers and peptic erosions. The incidence varied from 60 to 100%, depending on the amount of vitamin A in the diet. In these animals there was also a reduced amount of mucus secreted by the stomach (method of determination not stated). The pH of the normal stomach they found to be 3.4; in the stomach with ulcers it was found to be between 2.5 and 3. When Fogelson's mucin was fed, it seemed to have some beneficial effect on the stomach, but it did not prevent death from the vitamin deficiency. Incidentally, a high incidence of microscopic gastric ulcers has been found in rats fed a vitamin B₁ deficient diet⁷⁰ and about 25% of a series of 75 guinea pigs fed diets deficient in vitamin C developed macroscopic ulcers in their stomachs.⁷¹

Turner and Loew⁷² noted gastric dilatation in their monkeys which had died from A avitaminosis. Manville⁴⁵ reported that after about 2 months on an A deficient diet the rat's mouth, large bowel, rectum and feces became drier, probably due to a lack of glandular secretion, and pH of the saliva changed from the normal 7.4 to 6.6. Debré, Bussón and Simmonet⁷³ found hemorrhages into the stomach, intestines and bladder in their A deficient rats and the extent of the bleeding increased with the severity of the deficiency.

Even as little as 3 weeks on an A free diet is usually sufficient to cause changes in the intestinal tract which are visible to the naked eye, according to the recent work of Richards.⁵ She observed with great frequency keratosis and ulceration in the squamous part of the stomach, and pittings, hemorrhagic points and even ulceration in the glandular part. These changes as well as those found also in intestinal tract (see below) this author thinks are responsible for most of the decreased rate of growth in such animals.

A good many years prior to this Cramer⁷⁴ (1923) had found marked atrophy of the villi with necrosis of their tips in the lower ileum of animals fed diets lacking the fat soluble vitamins, when compared with controls fed either a barely adequate or a vitamin rich diet. These changes he thought would lead to decreased absorption of the food. This same author, with Kingsbury,⁷⁵ found that in this deficiency the mucous glands of the intestine atrophy and there is of course a decrease in the amount of mucus. This favors bacterial multiplication, and he observed that the bacteria which normally are almost restricted to the central lumen, in these avitaminotic rats penetrate between the villi into the crypts of Lieberkühn and into the mucous glands of the cecum, which they fill and where they proliferate. Wolbach and Howe⁷ noted

a very slight atrophy of Brunner's glands. De Ruyter has recently also found atrophy of the mucous glands, and in addition the disappearance of the goblet cells in the intestine. Some years ago, MacKay⁷⁶ found that when kittens were kept on diets deficient in the fat soluble vitamins they developed diarrhea and abdominal distention and the intestinal wall was found at autopsy to be very thin.

Several authors have found that diarrhea commonly occurs when animals are fed such diets. Nicholls⁵⁶ and also Pillat⁵² observed diarrhea in human cases of keratomalacia, where it came on some time after the eye changes began. Wolfe and Salter²³ observed it in mice, Hart *et al.* in cows,²⁶ Turner and Loew⁷² in monkeys, and Gudjónsson⁴⁵ in a few rats at the terminal stage. In the monkeys it was very severe and ended in death, and at autopsy the intestines showed marked enteritis. Tilden and Miller^{22b} regularly found that monkeys developed diarrhea and colitis on A deficient rations. When the monkeys were examined after death a few showed gross ulcers in the colon, more showed microscopic ulcers and severe colitis, and a few showed less severe lesions. Two monkeys showed no changes in the intestine. On the other hand, Hetler^{22a} observed colitis in only 3 of his 27 A deficient monkeys, and 2 of these had intestinal ulcers with inflammation or edema of the intestinal mucosa. He thinks that the colitis observed by others in monkeys may have been due to the use of an irritating diet. The monkey apparently is prone to develop diarrhea. Seifried¹⁸ observed intestinal catarrh and inflammation in adult hens fed A free diets.

Richards⁵ has recently reported a strikingly high incidence of cecal inflammation in rats on A deficient diets. Ulcers of the cecum were also quite common, as well as inflammation of the duodenum and the rest of the small intestine. Diarrhea, especially in the later stages, was not infrequent. There was apparently no epidemic of enteritis and the controls were unaffected. One would infer that infections had been set up in the intestinal mucosa which had been rendered more vulnerable by the food deficiency. Richards' report is based on large series of rats and should be repeated by other investigators. Green and Mellanby⁷⁷ had an epidemic of enteritis during the course of their experiments and their vitamin A deficient rats were very susceptible, 21% of them dying.

Ackert and his collaborators⁷⁸ noted more material than usual in the intestines of their A deficient chickens, which suggested sluggish peristalsis. Gross,⁷⁹ by means of feeding charcoal to rats and identifying it in the feces (a method which the present author found unsatisfactory), found that material passed more rapidly than normal through the intestines of A deficient rats. Seidmon and Arnold⁷⁹ demonstrated that the intestinal tract of A deficient rats was more permeable to bacteria, as determined by feeding the organisms and culturing several organs after $\frac{1}{2}$ to 1 hour intervals than was that of adequately fed controls.

Working with young children and infants, Rowntree⁸¹ demonstrated that much vitamin A is excreted in the feces. In 2 of the infants fed a diet low in vitamin A, the excretion exceeded the intake. Perhaps the excretion of vitamin A by the intestinal mucosa may provide the cells with this factor, so that they locally do not suffer from a lack of

this factor and do not show metaplasia. No vitamin A was found in the urine even though generous amounts were fed. Von Drigalski⁸² found vitamin A in the feces of rats when they were fed it in excess. In human beings he did not find it in the feces.

Sweet and K'Ang,⁵⁸ who carried out 17 autopsies on Chinese patients suffering from avitaminosis A, found in 5 that the esophagus showed hyperkeratosis (like epidermis). The submucosa was infiltrated with a moderate number of lymphoid cells and a few mononuclears. The digestive tract otherwise was normal.

Urinary System. According to the work of Wollbach and Howe the epithelium of the renal tubules showed no metaplastic change. Mendel¹⁵ stated that the cells of the renal tubules seem to become calcified in some instances when rats are deprived of vitamin A for long periods. De Ruyter⁹ has recently published a photograph of such calcified epithelial cells. van Leersum,⁸³ using rat diets which were probably deficient in both vitamins A and D, found calcium deposits very commonly in the kidney tubules. This finding was very rare in the adequately fed controls. Davis and Outhouse⁸⁴ fed their rats a diet which was partially deficient in vitamin A and probably free from vitamin D. They found cloudy swelling of the parenchyma of the collecting tubules, which was especially well seen in the second generation raised on this diet. Sometimes an albuminous precipitate was seen in the tubules. The bloodvessels were also congested. Gross⁷⁹ reported that in vitamin A and D deficient rats there was a greater incidence of vacuolation of the cells of the convoluted tubules near the pyramids and more marked congestion than normal. In a series of only 7 rats which were fed an A and D free diet, Frontali⁸⁵ found 4 with macroscopic abscesses, 2 with microscopic abscesses and 1 with perivascular hemorrhages in the kidney substance. Other investigators have not as yet confirmed this work. Chu and Murphy⁸⁶ state that in the early stages of vitamin A deficiency their rats did not show any reduced kidney function as measured either by the excretion of creatinin or by specific gravity determinations on the urine.

Quite a number of detailed studies have been made on the changes in the kidneys of chickens subsisting on suitable A free diets. Elvehjem and Neu⁸⁷ found that in such birds many of the renal tubules were dilated with urates and the whole kidney seemed to be filled with this material. The blood uric acid was raised, probably because of the kidney damage. There was always slight nephrosis and occasional areas of parenchymatous degeneration, mostly in the proximal convoluted tubules. The distal portion of the collecting tubules and the ducts of Bellini were considerably dilated. Some of the tubules contained leukocytes, giant cells and cellular debris, others considerable colloid material. Practically all the sections showed hyalin deposits in both arteries and glomeruli. Birds do not destroy uric acid and convert the greater part of the urea into uric acid for elimination. Beach⁸⁸ reported similar gross changes. Capper⁸⁹ and his co-workers found that chickens dying of vitamin A deficiency showed white, powdery deposits, apparently of urates, around the heart, liver and other organs, which agricultural experts diagnosed as visceral gout. Emmett and Peacock⁹⁰ reported similar findings and also that the kidneys were usually very pale and marked with a network of very fine

white lines, which were urate filled tubules. These workers, particularly Elvehjem, have demonstrated clearly that severe vitamin A deficiency caused definite pathologic changes in the kidneys of chickens. Similar intensive studies on the rat would be of interest.

Many authors have described metaplastic changes in the kidney pelvis of animals and even of man. Tyson and Smith⁹¹ noted that these changes might appear early, even preceding those in the respiratory tract. They found that the epithelium first was piled up (hyperplastic) and the subepithelial tissue infiltrated with neutrophils. The epithelium later became keratinized. Harris and his co-workers⁹² also described hyperplasia in the pelvis epithelium. Another frequent site of hyperplasia in the metaplastic epithelium is at the base of the tongue. Rats fed vitamin A free diets commonly develop pyelitis. Richards, for example, found that 45% of 64 rats fed such diets for 5 to 11 weeks developed such infections.

Metaplastic changes in the bladder epithelium are also common. Arons and van der Rijst⁶⁷ state that the changes always begin at the urethral orifice. If the rat is kept on the diet long enough, one-third to one-half of the bladder is affected, and later all of it. The keratinized epithelium shows verrucose thickenings. These authors found that these epithelial changes sometimes occurred without associated infections. Harris and his co-workers⁹² thought that they had possibly found slight metaplasia without infection sometimes in the sublingual and submaxillary gland. These processes were, however, very usually found together and the infectious process never preceded the metaplastic. Frontali found epithelial pearl formation in the metaplastic epithelium of the bladder and, in his rats, cystitis was even more common than pyelitis. Bliss and his associates⁹³ found that if rats were fed diets lacking only vitamin A their bladders became distended and badly congested and some abscesses were found in the bladder walls.

Fujimaki⁹⁴ and also Higgins⁹⁵ state that the urine of rats fed vitamins A and D deficient diets becomes alkaline. If the missing vitamins are added the urine becomes acid again. It has been suggested that the alkalinity is due to infection with organisms, *e. g.*, staphylococci, streptococci or *B. proteus-ammonia*. The latter is known to convert urea into ammonia and carbonic acid, which would probably explain the more alkaline reaction. However, Higgins found alkaline urine regularly even before infections were demonstrated. van Leersum⁹³ reported that the urine was acid and he rarely found cystitis, or bacteria in the urine. Hematuria was, however, fairly common. Further simultaneous measurements of the urinary pH and accurate bacteriologic tests under such dietary conditions are indicated. Possibly some of the beneficial urine acidifying effects of ketogenic diets may be due to their high vitamin A content.

Considering the exfoliation of epithelial cells which may occur in either the pelvis of the kidney or the bladder, it is not surprising that several authors have noted an increase in the epithelial cells in the urine in human cases of keratomalacia.^{62, 96} Chu and Murphy⁹⁶ also noted that 88% of a series of rats suffering from early vitamin A deficiency had increased numbers of epithelial cells in the urine.

The question of the relation of vitamin A to urinary calculi is at present in an unsettled state. As a short but comprehensive review on

the subject has recently appeared in the *Journal of the American Medical Association*,⁹⁷ this discussion will be brief. It is true that a good many of the authors who claim to have produced calculi in rats by a lack of vitamin A have as a matter of fact used diets deficient in vitamins D and C as well. However, as the rat can apparently synthesize vitamin C, it does not need this in its diet. As to the lack of vitamin D, Bliss and his co-workers⁹³ demonstrated that a diet deficient in vitamin A alone was just as effective as one lacking both vitamins A and D for the production of calculi. If vitamin A alone was added to the A and D free diet, calculosis did not occur. Also Higgins⁹⁵ found that diets deficient in vitamin D alone did not give rise to calculosis. It therefore seems reasonable to suppose that the associated deficiency of vitamin D has no effect, and that vitamin A is the important factor. Also Arons and van der Rijst found that 13% of their rats developed vesical calculi when they were fed a diet deficient only in vitamin A. The problem of lithiasis is further complicated by the fact that if excessive phosphates or especially calcium salts are added to the diet the incidence of stones increases markedly.⁶⁷ In addition McCarrison⁹⁸ showed that a diet devoid of fat-soluble vitamins and high in calcium (also low in good proteins) frequently caused calculosis. The addition of neither phosphates nor vitamin A alone prevented the formation of the stone, but if both these substances were added simultaneously no stones were formed. In other words, McCarrison showed that urinary stones could be formed when vitamin A was present in the diet. Other investigators^{99, 100} have also found this to be the case. In 2 cases the Ca/P ratio in the diet was abnormally high,^{98, 99} and in the third an excess of magnesium carbonate was fed.¹⁰⁰

When the rats are fed diets deficient in vitamins A and D, the stones are almost always composed of phosphates of calcium and magnesium with a little organic material and possibly traces of oxalates of potassium and sodium. In man the problem is more complicated as several varieties of stones (urates, phosphates, etc.) may occur. As a general rule rats must be kept on the deficient diets for long periods, with short intervals on a normal diet to keep them alive, before the stones appear. The cystic stones appear first, later followed by renal stones and finally by stones in the bile ducts.⁹⁴ The latter are formed largely of cholesterol and pigment. Emiliani and Bazzocchi¹⁰¹ reported that 75% of their guinea pigs fed an A deficient diet developed biliary calculi. When a vitamin B deficient diet was used, no biliary calculi were formed.

No adequate theory has been proposed to explain why a deficiency of vitamin A leads to the formation of urinary stones. Some of the factors involved may be as follows:

1. The sloughed off keratinized cells may provide nuclei for the stones.
2. The drainage of the urine may be interfered with, due to epithelial proliferation in the ureters or urethra.
3. This stasis of the urine may favor infection. Infection very commonly accompanies calculosis.
4. The alkaline reaction of the urine, due perhaps to bacterial changes, may allow the salts in the urine to be precipitated out of solution.

Genital System. *In the Male.* In 1925, Wolbach and Howe⁷ reported that in rats which had been fed a vitamin A deficient diet

for some time, the testes were only about half their normal size. About a year earlier Gross⁷⁹ had noted the same atrophy. However, early in the course of the deficiency the testes showed marked edema. Thatcher and Sure¹⁰² only occasionally observed edema beneath the capsule and extending slightly between the glands. They noted in addition that general or local atrophy of the tubules was common. Wolfe and Salter²³ found that in mice the testes were small, soft and watery when cut. Manville⁴⁵ found the seminal vesicles underdeveloped in his vitamin A deficient rats.

Metaplastic changes in the epithelium of the epididymus, prostate, seminal vesicles and Cowper's glands have been described in both the rat⁷ and the guinea pig.²⁴ Similar changes in the last three organs were also found in the mouse.²³ In man, Sweet⁵⁸ observed metaplasia of the prostate in 1 of 10 cases of keratomalacia. Abscesses may later occur in the seminal vesicles and prostate and preputial glands according to Arons and van der Rijst.⁶⁷

Goldblatt and Benischek¹⁶ found atrophy and degeneration of the germinal epithelium and Wolfe²³ described somewhat similar changes in mice. A really detailed investigation was published by Sampson and Korenchevsky¹⁰³ in 1932. They described changes similar to those found in vitamin E deficiency with the formation of giant cells. However, from the excellent work of Mason^{104a} which appeared in 1933, it appears that Sampson's diets were likely deficient in vitamin E as well as vitamin A. A deficiency of vitamin A seems to accentuate the need for vitamin E. In vitamin A deficiency only, Evans^{104b} and also Mason found that the testes changes occurred before or at about the same time as xerophthalmia and frequently before any loss in body weight. The earliest change consisted in marked sloughing of the germinal cells into the lumina, with a consequent reduction in the tubule size. Often there were small numbers of deeply staining pyknotic cells visible. The epithelium seemed capable of slow cellular differentiation and sperm production for a considerable period of time in spite of the marked reduction in tubule size. The tubules usually contained from one to four layers of germinal cells, mostly spermatogonia and very immature spermatocytes with a few more mature cells attempting to produce sperms and a few poorly formed sperms. As the degeneration progressed spermatogenesis stopped, and in the final stage the picture was very similar to that of the last stage of vitamin E deficiency, although in the latter there is usually a more complete removal of the residual germ cells. These changes in the germinal epithelium are of course not those of keratinization.

The poor nutritive state of the animal probably results in the decreased production of the sex stimulating hormones of the anterior pituitary, which in turn leads to atrophy of the accessory sex organs.

In the Female. Wolbach and Howe found metaplastic changes in the epithelium of the oviduct and uterus in the rat⁷ and guinea pig,²⁴ and such changes have been found in the latter organ in man.⁵¹ The altered uterine epithelium may explain the frequently observed sterility in A deficient rats.¹⁵ The cause may, however, be a partial or complete blocking of the oviduct with desquamated epithelium. Evans¹⁰⁵ found that about one-fifth of the copulations of A deficient females resulted in pregnancy, and that the young which were born were normal. When

pregnancy did not result, there was no evidence that implantation had occurred and in some cases where sections were made of the oviducts 1 to 3 days after copulation, degenerating ova were found which showed no signs of fertilization or cell division. Manville⁴⁵ and others also thought that fertilization and implantation often did not occur. Sure,¹⁰⁶ on the other hand, found evidence "by the resorption curve" and by the appearance of the uterine horns, that the rat fetus had been resorbed during gestation. One would suspect that this was due to an associated deficiency of vitamin E. It has been observed that the normal phenomenon of pseudopregnancy does not occur in vitamin A deficient rats, which suggests that there is some impairment in the internal secretions of these rats.¹⁰⁵ Hughes and his collaborators²⁵ regularly found that sows fed A deficient diets and bred before the onset of nervous symptoms always aborted or gave birth to dead young.

It is probable that no changes occur in the ovaries of rats fed vitamin A deficient diets, as Drummond,^{102,107} Coward¹⁰⁸ and Thatcher and their co-workers have found. Opinion, however, is not unanimous on this question as Gross⁷⁹ found in the rat that more Graafian follicles than usual were degenerating, and in the guinea pig, Wolbach and Howe²⁴ consistently found atrophy of the ova and Graafian follicles. Further detailed studies of the ovaries of such animals would probably clear up the question.

In 1922, Evans and Bishop¹⁰⁹ observed that in female rats fed diets deficient in vitamins A and D the vaginal smears, which normally consisted of cornified epithelial cells only for about 30 hours during estrus, became persistently chiefly if not exclusively composed of these cornified cells. However, these workers observed that such animals continued to ovulate and to form corpora lutea irregularly or at intervals approximately normal. Evans¹⁰⁵ later studied this problem by observing the behavior of such females in the presence of normal males, by examining their ovaries for presence of ripe follicles, and by removing both ovaries and then examining the vaginal smears. At times when only cornified cells were present in the smear, the females did not copulate, and ripe follicles were absent. Also the continuous cornified smears appeared even when the ovaries were absent. In other words, these vaginal changes were unrelated to the ovary. The addition of vitamin D to the diet did not alter the reactions. Aberle¹¹⁰ made sections of the vaginas of such animals and found that the peripheral cells of the vagina were cornified, and in many instances leukocytes were seen between the cornified cells. She also noted that at about the time the continuous cornified smears appeared, the vagina was very dry, and that the vaginal mucosa could not produce mucus even after the injection of excessive amounts of placental extract. In normal rats this treatment causes large amounts of mucus to be secreted. Mason¹¹¹ later reported that mucus production in the vagina ceased in these animals. In fact this author made the general observation that the ability of epithelial cells to produce mucin was lost in vitamin A deficiency, whereas that of producing keratin was increased. He suggested that vitamin A had some controlling influence on protein metabolism in the epithelial cells. He also noted that no preliminary atrophy occurred in the vaginal epithelium in these rats. The vaginal epithelium increased greatly in thickness, which fits in with the finding,

previously reported by Aberle,¹¹² of increased mitotic activity in this tissue in castrate rats. In the normal rat, at the approach of pro-estrus the superficial layers of the vaginal epithelium are nucleated, and these cells appear in the pro-estrus smear. Beneath this is a cornified layer which is shed during estrus. In the deficient rats the superficial layer becomes cornified, and the normally cornified layer becomes wider. It is less completely removed immediately after estrus, and this, plus the abnormal cornification of the deeper layers, leads to the appearance of cornified cells in the di-estrus smears.

Mason¹¹³ also examined the vaginal smears of rats fed the A deficient diet and of controls whose weights were kept at approximately the same levels by feeding reduced amounts of a complete diet. He stained the smears supravitaly with neutral red which enabled him to demonstrate the estrus cycles despite the abnormal cornification. The estrus cycles became definitely longer and irregular when the animals showed retardation or decline in growth, regardless of whether the deficient or restricted adequate diet was fed. The effect on estrus was therefore due to inanition only. However, the abnormal cornification occurred only in the rats fed the vitamin A deficient diet and was apparently the specific effect of this lack.

It has been stated that the appearance of continuous cornified vaginal smears is the first sign of vitamin A deficiency. This has not been found to be regularly the case,¹⁰⁹ although it may occur in some 40% of the animals before cessation of growth.⁸⁶ It does precede xerophthalmia, and as growth retardation is not a specific effect, it has been used as a means of testing for vitamin A. Turner and Loew⁷² observed that after monkeys had been fed such diets for about 60 days their vaginal smears showed persistent cornified cells and the menses ceased. Hart²⁶ also observed that at the end of a very dry summer the cattle on a certain ranch developed night blindness, corneal ulcers, diarrhea and the non-recurrence of estrus after calving. Calves born late in the season died. The survivors recovered when green feed was available again. Manville⁴⁵ also noted lessening of the mammary secretions due to incomplete development and decreased function.

It has been found that 3 to 5 γ of carotene (pro-vitamin A) will cure the specific ophthalmia and cause slow growth, but the vaginal smears still remain abnormal.¹¹⁴ If 10 γ is given, di-estrus smears appear within 1 week, and estrus within 2 weeks. That vitamin A is very essential for reproductive activity has also been shown by Manzi¹¹⁵ who found that larger amounts of carotene were required by a pregnant guinea pig on a diet free of vitamin A to bring the pregnancy to a successful termination than for maintenance of a non-pregnant animal on the same diet.

Spleen. Several authors have made brief references to the changes occurring in the spleen in vitamin A deficiency. For example, Davis and Outhouse⁸⁴ found only very slight changes in the spleen, such as congestion and frequent dilatation of the venous sinuses, in rats which were fed diets partially deficient in vitamin A. Wilson and Du Bois⁵¹ noted that the spleen of an infant that died apparently of this avitaminosis had splenic nodules with very pale centers, in which large mononuclear cells with abundant protoplasm were numerous. The same changes were noted in the mesenteric glands and Peyer's patches.

Gross⁷⁹ stated that his rats showed a great increase in thickened hyalin bloodvessels and pigment. Wobach and Howe⁷ noted a great diminution in the size of the spleen which was due to the depletion of the lymphoid cells and erythrocyte forming cells. There was, however, an increase in phagocytic cells laden with hemosiderin. They also remarked that the same changes were found in vitamin B deficient rats. These same authors later stated that guinea pigs showed no change in the size of the spleen, but it contained heavy accumulations of hemosiderin in the phagocytic cells. Blackfan and Wobach²¹ found hemosiderosis in the spleens of all the infants, apparently dying from this deficiency, that came to postmortem, and Sweet and K'Ang⁵⁸ found it in half their adult cases of keratomalacia. These investigators thought that the hemosiderosis, which occurred frequently in other conditions, was not a specific effect of the deficiency. Thatcher and Sure¹⁰² reported that the spleen showed atrophy; Bliss *et al.*⁹³ that it was discolored and in most cases shrunken and infiltrated with fat; and Wolfe and Salter²³ that it was usually very dark and small.

A very detailed investigation was published by De Ruyter⁹ in 1934, including excellent photographs of the histologic changes in the spleen. In early deficiency the spleen is macroscopically normal. Microscopically, the Malpighian bodies are easily made out and it is seen that the central area, which is much wider than usual, is composed of many large, markedly phagocytic cells and a few lymphocytes. The outside zone is smaller than usual and contains a smaller number of small lymphocytes and a larger number of large and medium-sized lymphocytes and histiocytes. At the periphery of the spleen the cells are larger and swollen and show mitosis. Also numerous free histiocytic cells and marked phagocytosis is seen here, which would suggest that there was stimulation rather than atrophy, although the small lymphocytes have partially disappeared. This deficiency of lymphocytes is also evident in the atrophy of the Peyer's patches and of the solitary follicles, and in the white blood picture.

In marked vitamin A deficiency, the spleen is very small and thin and the Malpighian corpuscles can hardly be made out. On high magnification it is seen that in the central areas of the corpuscles there are large swollen reticular cells, numerous small and medium-sized lymphocytes, occasional free histiocytes and a number of large macrophages full of blood breakdown products. The germinal center is therefore in an active phagocytic state. Lymphocytes are very scarce in the next layer. The periphery of the spleen appears inactive and no evidence of mitosis is seen. In some places remains of red blood cells and a few intact red cells are seen. The histiocytes are rare and where they are found they are laden with detritus and pigment.

When trypan-blue was injected, the ability of the reticulo-endothelial cells of the spleen to accumulate it was very markedly reduced.

Rydh-Ehrensward and Schmidt¹¹⁶ reported that the guanase activity of the spleen was lowered in rats on an A free diet and also that the activation period of the enzyme was also changed. Carotene feeding raised the guanase content of the spleen and restored the activation period to normal.

Lassen¹¹⁷ showed that rats fed vitamin A and also A and D deficient diets were considerably more susceptible to *B. aertrycke* infections

whether they were inoculated *per os*, subcutaneously, intravenously, or intraperitoneally, than were normal controls. With the last three methods, the effect of the possibly increased permeability of the mucous membranes is ruled out. With oral infections he found that in the normal controls the bacteria were localized for the most part in the Peyer's patches and mesenteric glands, with some extension to the liver and spleen. In the avitaminotic animals the liver and spleen were regularly involved and a fatal bacteremia followed. These results might be explained on the assumption that the reticulo-endothelial system was not functioning efficiently.

Crimm *et al.*¹¹⁸ also noted that after the injection of *B. typhosus*, vitamin A deficient animals had a more persistent leukocytosis than did either the controls or the moderately deficient animals. It would appear then that the ability of the reticulo-endothelial system to fix and dispose of foreign protein is reduced in this deficiency.

Liver. Several authors have reported that no changes occur in the liver of vitamin A deficient animals; for example, Wolbach and Howe²⁴ using guinea pigs, and Wolfe *et al.*²³ with mice. Davis and Outhouse⁸⁴ also found that the livers of partially deficient rats were normal. On the other hand, Gross⁷⁹ reported great congestion in the liver, and Wolbach and Howe⁷ noted diminution in size, which they thought was due to the absence of stored fat and glycogen. These investigators used white rats. Thatcher and Sure¹⁰² found in about one-third of their deficient rats that there was fibrosis about the portal spaces, and infiltration with eosinophils and small lymphocytes. Only one of their controls showed a similar but less marked reaction. De Ruyter⁹ later independently reported fibrosis in these same areas. Bliss and his collaborators⁹³ noted that the liver was discolored and frequently shrunken and infiltrated with fat, and Blackfan *et al.*²¹ and also Sweet *et al.*⁵⁸ described hemosiderosis in the liver as frequently as in the spleen.

De Ruyter⁹ also gave a detailed description of the liver changes. Macroscopically only 24 of the 178 livers examined showed changes which could be ascribed to the deficiency, such as diffuse swelling and a yellowish-brown color. Microscopically, of 42 livers examined only those in the very early stages of the avitaminosis showed no changes. In the others, the liver cells contained either large or small vacuoles, apparently of fat. The nuclei were sometimes pyknotic and sometimes did not stain well. In the early stages the fat appeared only in the cells about the periphery of the lobule, but later these changes were generalized. The glycogen disappeared from the liver cells. The fibrosis around the bile ducts occurred only rarely. Changes in the Kupffer cells, which occurred early and regularly, consisted in swelling, deposition of fat and pyknosis of the nuclei. When trypan-blue was injected the Kupffer cells absorbed it very poorly. Leber,¹¹⁹ in 1883, described a human case of keratomalacia in which the liver was fatty.

Saiki¹²⁰ tested the excretory functions of the liver of rats and monkeys fed normal and vitamin A and D deficient diets by injecting Azorubin S intravenously and then determining how soon it was excreted by the bile and how long the bile contained it. In the deficient animals the dye was excreted much less rapidly, although the time of appearance in the bile was not much altered.

Drummond and his co-workers¹²¹ injected a colloidal solution of

carotene intravenously into cats. They found that the greater part of it was immediately absorbed by the liver where it was found exclusively in the Kupffer cells. It is well known that in the normal animal the main store of vitamin A is in the liver.

Blood. As regards the number of red blood cells, several authors (Happ,¹²² Turner,¹²³ Falconer¹²⁴) state that this is unaltered in vitamin A deficiency; Damianovich¹²⁵ found it reduced. Cramer, Drew and Mottram¹²⁶ reported that in the early stages there was no constant difference, but that in the advanced stages anemia was present. Koessler and his co-workers¹²⁷ were able to cause a blood picture similar to that of pernicious anemia by feeding deficient, adequate, deficient and finally adequate diets. This has apparently not been confirmed by other investigators. Davis and Outhouse⁸⁴ gave their rats a diet low in fat soluble vitamins and found marked anemia in the second generation. Frank¹²⁸ has recently reported a decrease of 25% in the red cell counts of rats fed a diet deficient in vitamins A and D and consisting of oats 40, extracted casein 5, dextrin 52.5, NaCl 1, and CaCO₃ 1.5. It is possibly also a little low in the vitamin B complex. The blood was obtained by heart puncture. Mouriquand and his co-workers¹²⁹ also report anemia in vitamin A deficiency.

Whether the white blood count is altered in vitamin A deficiency is still an open question. At least three authors^{118, 126, 130} have reported no change. On the other hand, Falconer¹²⁴ found a rise of about 20% and Turner and Loew¹³¹ noted that from the stage of moderate xerophthalmia on, there was a progressive and marked rise in the white blood count. One would associate this with the frequent epithelial infections. Frank,¹²⁸ however, states that the leukocyte count is decreased in A deficient rats. Children with xerophthalmia on the contrary had a much increased white blood count, which was reduced about 50% after a short time on a high vitamin A diet. Several authors^{128, 130, 131} have noted that the per cent of neutrophils increases, with a corresponding decrease in the lymphocytes. One of these investigators,¹³¹ however, found that this did not always occur, even in advanced deficiency. Crimm and Short¹¹⁸ have recently made the interesting observation that the percentage of senile granulocytic cells is increased. Apparently then a lack of vitamin A inhibits the formation of these cells. If vitamin A were given to one of these deficiently fed animals, there was marked increase in younger cells.

There is also considerable variation as regards the platelet counts. Kugelmass¹³² and Frank¹²⁸ found them unchanged. Falconer¹²⁴ and also Bedson and Zilva¹³³ found a reduction of about 20%, which the latter authors did not consider specific. In the earlier work, Cramer and his associates¹²⁶ found a marked thrombopenia, which they thought was caused by the platelets adhering to bacteria which were frequently present in the blood stream. Later investigators rarely were able to culture bacteria from the blood.¹³¹

Falconer¹²⁴ found no definite change in the hemoglobin, whereas Frank¹²⁸ reported a decrease of 27%. Falconer¹²⁴ also stated that the blood volume was reduced.

In rats, Kugelmass¹³² found the fibrinogen content of the blood markedly lowered and the bleeding time prolonged. In similar animals Frank¹²⁸ found the fibrin content much reduced, the clotting time

increased, and the bleeding time at least doubled. He thought that these alterations were due to degenerative processes in the liver. In 2 infants suffering from xerophthalmia he found that the bleeding time was not increased although the plasma fibrin was down considerably. Simola¹³⁴ noted a much increased clotting time and much reduced lipase content in the livers of A-avitaminotic guinea pigs.

According to Binet and Strumza¹³⁵ the recovery of dogs from anemia due to bleeding is much helped by carotene *per os*. No vitamin A is found in the red blood corpuscles of the dog, but only in the plasma.

Teeth. Smith and Lantz¹³⁶ investigated the gross changes occurring in the incisor teeth of rats fed vitamin A free diets. At about the time that growth ceased and early signs of eye infection occurred, the teeth gradually lost their normal orange pigment and luster. They became short and blunt, and at death were found to be very friable. Measurements showed that the tooth growth was markedly retarded, in fact almost inhibited completely as death from vitamin A deficiency approached. If cod liver oil was given to the vitamin A depleted rats which had shown the above changes, the teeth grew normally again and regained their normal appearance and hardness. These authors also determined the percentage of ash, calcium and phosphorus in these teeth and those of controls fed the diet plus cod liver oil. The teeth of the rats fed the deficient diet contained 2% less ash, 4.4% more calcium and 0.8% less phosphorus, and it is suggested that less calcium was deposited with the phosphate radical and a larger proportion as the carbonate or in some other combination, which possibly explained the increased friability. Wolbach and Howe¹³⁷ noted the same changes, but thought that the loss of the normal orange pigmentation and the acquisition of the chalky white appearance were due to the loss of the enamel which is pigmented, and to a change in the composition of the dentine. Gudjónsson⁴⁶ had previously found the teeth of A deficient rats more friable than those of normal animals.

Shibata,¹³⁸ in an article that was apparently poorly translated into English, described in 1931 the appearance of the teeth of albino rats fed such deficient diets. They showed abnormal formation of the enamel, dentine and cementum, and atrophy and abnormality in the enamel organ, dental pulp and root membrane tissue. The incisors were erupted late and there was increased cornification of the epithelium of the gums. Simola¹³⁹ found marked histologic changes in the teeth, particularly in the odontoblasts and pulp tissue.

In 1933 Wolbach and Howe¹³⁷ published an excellent account of the changes produced in the incisors of rats and guinea pigs by diets deficient in vitamin A. The first changes appeared in the enamel organ, which is just outside the enamel and mostly on the labial side. It consists normally of an inner layer of higher columnar ameloblasts and outside this are small epithelial papillæ separated by vascular connective tissue. The papillæ first atrophy and the connective tissue becomes less vascular. The ameloblasts become smaller, then granular and finally disappear, and are replaced by two rows of flat cells, probably arising from the stratum intermedium. In very late stages of the deficiency these develop numerous layers of flat cells and may be keratinized. Deposits of calcium commonly appear in the connective tissue between the papillæ in the late stages in the guinea pig, but are

quite rare in the rat. These later take on the appearance of bone in the guinea pig.

At the same time as these changes are occurring in the enamel organ, the odontoblasts, which form the inner layer of the dentine, show atrophy. In the rat the odontoblasts on the labial side survive much longer than on the other sides, and as a result the dentine on this side is very much thicker than elsewhere. In the guinea pig, all the odontoblasts atrophy at the same rate. In the rat, when the atrophy is complete, the inner surface of the dentine is bounded by cells undistinguishable from the rest of the pulp cells. In the depths of the pulp small areas of osteoid tissue are frequently found in the late stages of the deficiency. Sometimes small glandlike clusters of ameloblasts are found within folds of thin dentine. These ameloblasts and also odontoblasts that have lost their polarity, probably because the normal ameloblasts have atrophied, form deposits of dentine-like material.

In the guinea pig the changes were similar except that the odontoblasts did not completely atrophy, spicules of dentine grew into the pulp, and the cementum which resembled bone was thicker and showed small outgrowths at intervals on its outer surface.

From the study of the teeth of adolescent children who were blind as the result of xerophthalmia in infancy, Bloch⁶³ concluded that vitamin A had no effect on dental caries or formation.

Previous mention (see p. 413) has been made of the changes which M. Mellanby found occurring at the gingival margins. In addition, she found that the epithelial attachment to the poorly calcified enamel is often less perfect. It normally occurs at the amelo-cement junction, but tends to extend rootwards in animals fed diets low in vitamin A. Also the connective tissue of the ligaments may be less well defined.

Recently M. Mellanby and King³² have reported that in the teeth of puppies fed diets deficient only in vitamin A, the enamel is abnormal in color and texture, but no definite changes were seen in its minute structure.

At least three reports^{21, 140, 141} have been published on the changes in bone as the result of deficiency of vitamin A. Probably, as these authors state, the changes are non-specific and are due to inactive osteogenesis, which would be expected from the stationary or declining weight and arrested growth.

Other Tissue Changes. Several authors^{7, 24} have noted that the fat disappears from adipose tissue, even when non-vitamin A containing fat is present in the diet. In the rat,⁷ clinical signs and microscopic changes do not occur until the bulk of the stored fat has disappeared. Guinea pigs,²⁴ on the other hand, showed advanced epithelial changes when considerable fat was still present.

No mention has been made of the changes occurring in the eye as they have been thoroughly described by numerous authors.^{50, 52, 64}

Discussion. It is possible that vitamin A with its 5 unsaturated bonds may play an important rôle in the maintenance of a favorable oxidation-reduction potential within the body cells. Joyet-Lavergne¹⁴² has shown that either oxidation or reduction reactions can occur on the surfaces of the mitochondria or nucleolus. He maintained conditions as nearly normal as possible and let substances which changed color with oxidation or reduction penetrate into the living cells, which

he was meanwhile observing under the microscope. In a later study he used an antimony trichlorid solution.¹⁴³ A blue reaction (very probably due to vitamin A) was consistently seen on the mitochondria of a great variety of animal and plant cells. The intensity of the blue color varied in different cells, being very intense on the mitochondria of hepatic cells and very weak in the salivary gland cells of a species of insects. If a nucleolus was present it became blue also. In the livers of sea fish, lumps of pale blue were also seen in the cell cytoplasm, often in contact with the mitochondria, and the author suspects that the mitochondria convert other materials into vitamin A which is stored as a reserve in the liver cytoplasm. The vitamin A in the mitochondria could be responsible for the oxidation occurring in the solutions used in the earlier experiments. No detailed description of the author's method was given in these articles. If these findings can be confirmed they will be of great interest.

Oppenheimer¹⁴⁴ suggests that vitamin A or carotene acts as an oxidation catalyst by taking up oxygen at its numerous double bonds and then giving it up again to the substance to be oxidized. Franke¹⁴⁵ showed that the power of oleic and linoleic acid to take up oxygen was doubled by the presence of carotene, which lost its color in the process. Vitamin A, and other carotinoids which could not replace vitamin A in the animal's diet however, had the same property.

Summary. 1. It is well known that a deficiency of vitamin A causes columnar and other types of epithelium to be replaced by squamous keratinized epithelium.

2. In young animals fed vitamin A free diets, it has frequently been shown that the fibers, especially those in afferent tracts or nerves, show degeneration of the myelin sheaths. The nerve cells of these fibers also frequently show degenerative changes. It seems quite possible that these changes in the sensory nerves may be responsible for the epithelial metaplasia.

3. It appears that in light adapted eyes vitamin A, but no retinen, a component of visual purple, is present; in dark adapted, retinen is present, but only a trace of vitamin A. In intact eyes, visual purple is regenerated from vitamin A, some of which is lost in the process.

4. In human beings, several authors have described papular eruptions due to the plugging of hair follicles with cornified material, with atrophy of the sebaceous and sweat glands. This is often associated with other evidences of vitamin A deficiency.

5. Hyperkeratotic changes associated with either ulcers or papillomata have been found by at least six investigators in the squamous celled fore-stomach of rats. Inflammatory changes in the cecum and elsewhere in the intestine may possibly be caused by this deficiency.

6. In the chicken, degenerative changes in the kidney epithelium associated with the deposition of urates in the tubules have been found. A prolonged deficiency of vitamin A frequently leads to the formation of urinary stones. If the Ca/P ratio in the diet is abnormal, the incidence of calculosis increases.

7. A typical series of changes occurs in the male germinal epithelium, finally leading to the cessation of a spermatogenesis.

8. In the female, the cells in the vaginal smears which are normally found at the various stages of the estrus cycle are replaced continuously

or almost continuously by cornified cells. This is apparently not associated with changes in the ovary.

9. According to recent work, the spleen in early vitamin A deficiency shows a decrease in its small lymphocytes and an increase in the phagocytic cells, larger lymphocytes and histiocytes. Later there is marked atrophy, although the germinal center still shows active phagocytosis. The absorption of trypan-blue is markedly reduced. Other evidence suggests a reduced efficiency of the reticulo-endothelial system.

10. Except in the very early stages, the cytoplasm of the liver cells contains vacuoles of fat and the nuclei show degeneration. Similar changes, with that of swelling in addition, were regularly seen early in the Kupffer cells. These findings need further confirmation.

11. It is likely that there is a relative decrease in the lymphocytes and a reduced fibrin content in the blood.

12. In the teeth, marked changes including atrophy of ameloblasts and odontoblasts and the appearance of osteoid tissue in the pulp occurred.

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HYGIENE AND PUBLIC HEALTH

UNDER THE CHARGE OF

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CHANGING CONCEPTIONS OF THE PREVENTION OF ACUTE ANTERIOR POLIOMYELITIS.

Mode of Transmission.—Regarding conditions of transmission, certain facts seem to have been well established by experimental studies and epidemiologic observations. The disease is caused by a filterable virus which enters through the nose, and leaves through the nose or respiratory tract. Transmission is effected through the respiratory route by person-to-person contact, and the contact required is of the same order as that which is effective in other respiratory-borne virus diseases such as influenza, measles, chickenpox. The individual who is exposed to the virus, depending upon the amount of resistance developed, may harbor the virus temporarily (a) without symptoms—a “carrier” state; (b) with a mild illness and symptoms of indefinite character—Frost’s “possible abortive” cases; (c) with symptoms sufficiently developed to be characteristic and recognizable by those familiar with the syndrome, although the spinal fluid may be normal—Frost’s “probable abortive;” (d) with characteristic clinical course and positive spinal fluid findings, but without the occurrence of demonstrable paralysis—“frank abortive” or “non-paralytic” poliomyelitis; (e) with characteristic clinical course, positive spinal fluid findings, and any degree of paralysis from a transient muscle weakness to a total ascending paralysis of the Landry type—the typical paralytic poliomyelitis. These classifications are not mutually exclusive and merge

into each other.* *Because of the widely varying symptomatology and the lack of a dependable objective test, it is at present impossible to set up a satisfactory criterion of diagnosis that will include all cases of this disease.*

The ratio of carriers, mild and missed abortive cases in comparison with recognized abortive and paralytic cases is still a matter of speculation rather than of exact statement. Evidence already at hand is sufficient to indicate that although this ratio may be variable in different epidemics, in different geographic areas, and even in different seasons, the former far out-number the latter.^{1,3,4}

Prevalence.—If it be accepted that these facts have been established, then it follows logically that:

1, Attempts to measure prevalence by means of morbidity reports are subject to a considerable error variable with the recognition of the milder forms of the disease. This can be partially overcome by separate rates based upon paralytic cases alone.

2, Attempts to measure the mildness of the disease in a given place and time by means of the ratio between reported "paralyzed" and reported "non-paralyzed" cases is in like manner subject to an imponderable error.

3, Attempts to measure the severity of the disease in a given time and place by means of official case fatality rates are, for the same reason, unreliable because of the variable number of abortive and non-paralyzed cases included in the "total cases."

Careful epidemiologic field studies with definitions and methods stated as clearly as possible are necessary to obtain relatively dependable information. These observations must be kept in mind in reading official reports of recent outbreaks of the disease.⁵⁻⁹

Variability.—Even when due allowance is made for the errors mentioned above, there is considerable evidence to indicate that the manifestations of the virus vary in different areas, epidemics and times as Wickman pointed out some years ago. In parts of the United States it would appear that the disease has become clinically more apparent than formerly, that its symptomatology is not altogether constant, that in the past few years it has been somewhat less fatal in proportion to those frankly attacked than formerly,³⁻⁵ that it is tending to shift its incidence toward higher age groups,^{5,10-12} and that it may become highly infective even for adult groups.³ It is also notable that recent epidemics have originated in areas of the southern part of the United States which hitherto have been largely free from such experiences.

Isolation and Quarantine.—If it be accepted that the conditions of transmission are essentially as outlined, then it also follows logically that the spread of the disease in human populations cannot be effectively limited by the isolation of recognized cases and their immediate contacts, no matter how rigid the restrictions imposed may be. This does not imply that such procedure should be abandoned nor that it does not in some degree restrict the spread of the disease to the immediate environment of a known case. It suffers from the same inadequacies

* Paul, Salinger and Trask¹ suggest that (b) and (c) be grouped together on the basis of suggestive symptomatology and negative spinal fluid findings, and that (d) be included with (c) as frank poliomyelitis. The practical objection to this proposal is that spinal fluid findings do not necessarily parallel clinical severity,^{2,3,4} and lumbar puncture is not always an available or permissible procedure.

as does isolation and quarantine in the other respiratory-borne virus diseases, that is, the case is infectious for some days before the diagnosis is made, and unrecognized cases and carriers can spread the disease just as effectively as can known cases.

It seems then that exposure to the virus is probably inevitable for everyone sooner or later, just as it is with the virus of such diseases as measles, mumps and chickenpox. The preventive effort must be directed primarily *not toward reduction in spread, but to decrease the incidence of clinical attacks* with the concomitant risks. Fortunately in poliomyelitis the natural resistance of the vast majority of human beings to infection is sufficiently great *to achieve immunity without penalty*. In only one or two out of each thousand population exposed does the defense mechanism fail to the extent that paralysis results from the infection, and in only about one out of each five to ten thousand population or more is the paralysis fatal. It would seem that with only a little improvement the natural defense mechanism could be made adequate for a still greater proportion of individuals.

Efforts to accomplish this result have proceeded along three lines, namely, 1, temporary passive immunity conferred by convalescent serum, 2, active immunization by vaccination with attenuated or killed virus; 3, improvement in the defense barrier at the point of entrance in the nose by nonspecific means. A discussion of the present status of each of these procedures will be clarified if first a brief résumé be given of the present conception of the pathogenesis of the disease. For a complete review the articles by Fairbrother and Hurst,¹³ Schultz,¹⁴ and Faber¹⁵ should be consulted.

Pathogenesis.—The virus is neurotropic. It grows in nerve cells and propagates along their axones. The site of implantation and initial multiplication is the nasal mucosa, and very largely, if not entirely, the olfactory epithelium high in the nose lining in the superior meatus and the corresponding part of the nasal septum.* This the virus must reach in order to establish an infective contact.

Having gained a foothold in the olfactory epithelium and established initial growth, it propagates by way of the axones to the olfactory bulb. From the bulb it makes its way along the olfactory tracts to the hypothalamus. As it progresses it dies out in areas previously infected. It is unable to reach the cerebral hemispheres or the cerebellum in quantities sufficient to be demonstrable. It finds a better opportunity to survive proceeding toward the brain stem and spinal cord. It makes its way from above downward¹⁸ and may be demonstrated at successive

* This does not preclude the possibility that the virus may enter by other pathways, but the evidence strongly supports the idea that it is the natural and usual portal of entry. It seems quite unlikely that it can become implanted upon the intact mucous membrane of the gastro-intestinal tract and make effective contact into the nerve supply unless local injury predisposes the area.^{16,17} Bulbar paralysis in cases of poliomyelitis following tonsillectomy may be explained as due to effective contact of the virus with nerve endings in the injured tissue. In this connection it is interesting to note (Leake⁶) that in cases of poliomyelitis following the use of the Kolmer's vaccine in each instance in which the site of the injection and the site of the first paralysis is known, the latter occurred either in the limb injected or in the corresponding limb of the other side. In other words, the cells of the spinal cord first involved were at the same level as the injection, suggesting that the virus traveled directly by way of the nerves which supplied the area into which the injection was made.

levels in the anterior and posterior horns and even in the intervertebral ganglia.

It shows a particular affinity for the anterior horn cells upon which it exerts its maximum toxic effect. The perivascular cuffing of the small bloodvessels follows. The systemic invasion suggested by lymphatic hyperplasia is a secondary phenomenon due to the peripheral distribution of the virus out from the central nervous system probably along nerve pathways.

Although this conception of the pathogenesis of the disease rests largely upon observations made upon monkeys, it is consistent with knowledge derived from the study of other virus diseases and with the clinical, pathologic and epidemiologic manifestations of poliomyelitis in human beings.

Convalescent Serum.—The earliest attempts to prevent or check the progress of paralysis in human cases involved the therapeutic use of convalescent serum. It was based upon the observation that such serum, and indeed the serum from a considerable percentage of the adult population who have, to their knowledge, not had poliomyelitis, is capable of neutralizing the virus *in vitro*. Since at this time it was held that the virus gained access to the central nervous system through the blood stream and spinal fluid, with localization in the meninges, it was reasoned that if the serum were introduced sufficiently early in the course of the disease it would exert a protective effect. Flexner and Lewis,¹⁹ 1910, and Flexner and Amoss,²⁰ 1914–1917, reported that if the intracerebral injection of a monkey is sufficiently small in dosage and followed within 24 hours by convalescent serum intraspinally (2 cc.) one may in some instances prevent the development of symptoms.

Upon the basis of this very limited theoretic and experimental background, the use of convalescent or adult serum was advocated *in the treatment* of human cases and received extensive clinical trial. Injections of 10 to 20 cc. were usually made intrathecally at the time of the diagnostic lumbar puncture, frequently supplemented by additional amounts given intravenously and subcutaneously. It was evident that if the disabling sequelæ were to be prevented or ameliorated the treatment must be applied before nerve-cell destruction had taken place. Proponents of its use therefore advised that it be restricted to those cases in which it could be given in the preparalytic stage.

From a careful review of the results in a large series of cases treated by this procedure, Aycock and his collaborators in the Harvard Infantile Paralysis Commission (1928–1929)²¹ confirmed the opinion expressed by many others on the basis of more limited clinical trial, that the amount of paralysis and mortality was significantly lower in the treated, in comparison with untreated cases. It later appeared, however, that this difference was due to the fact that the treated cases were a specially selected group of preparalytic cases while the untreated were not. When the two groups were made as nearly alike as possible Kramer, Aycock, Solomon and Thenebe²² and Park²³ found that the statistical advantage in favor of the treated group disappeared.

Schultz and Gebhardt²⁴ have recently reinvestigated the therapeutic value of specific immune serum in experimental poliomyelitis in the light of recent studies which indicate that from the very beginning of the infection the virus is intimately associated with neurones and that

once it is established in the nervous system it is propagated largely if not entirely along axonal routes. As a result of a series of carefully controlled experiments on monkeys they conclude that a highly potent virucidal (specific immune horse and convalescent monkey) serum injected by various routes one or more days after inoculation of the virus is without demonstrable value in the treatment of experimental poliomyelitis.

Evidence derived from both clinical and experimental trial therefore failed to establish the value of this procedure. It remained to ascertain whether it was possible to confer some degree of temporary passive immunity and protection upon human beings by the injection of convalescent serum *before exposure*, that is, prophylactically.

Opportunity was afforded by the unusual outbreak which occurred among the personnel of the Los Angeles County Hospital in 1934. Kessel, Hoyt and Fisk³ gave prophylactic injections of convalescent and normal adult pooled serum to 892 employees and subsequently followed their attack rate in comparison with that of 3094 employees in the same institution who received no serum. Briefly stated there was no evidence to indicate that any protection was afforded. In fact the percentage attacked was higher among those who received the serum than among those who did not, due probably to the inclusion in the former group of a higher proportion of specially exposed persons.

Schultz and Gebhardt²⁵ investigated the question with monkeys. They administered immune (virucidal) serum of high potency by various methods and in varying dosage from a few hours to 2 or 3 days before the animal was experimentally infected. The results indicated that immune serum is far from being a dependable prophylactic agent. The authors cautiously conclude that a liberal amount of high titer immune serum may protect animals against small doses of virus by diminishing the amount on the olfactory mucous membrane free to initiate infection. Once infected, the serum-treated animals generally develop as extensive paralysis as do controls, indicating that once the virus becomes established in neurones it can no longer be effectively reached by the virus-neutralizing antibodies.

In view of this evidence it is clear that *convalescent or immune serum, even when prophylactically administered cannot be relied upon to confer even a temporary protection against infection.*

The Poliöcidal Substance in Human Serum.—These and similar observations have brought to the fore the question of the nature and function of the virus-neutralizing substances. It is well established that they appear or are increased in the blood of individuals who have passed through an attack of the disease, in the blood of monkeys surviving experimental poliomyelitis and of monkeys vaccinated with virus emulsions, living or killed. It is also true that they appear in the blood of adults who give no history of a previous attack of the disease. Jungeblut²⁶ has suggested that while they may result from contact with the specific antigens, they may also be of heterophil nature, arising from experience with other antigens. Be that as it may, their presence in serum is not synonymous with immunity.

Schultz and Gebhardt²⁷ and others have demonstrated that monkeys immunized with virus emulsions and showing as a result virucidal properties in their serum can be readily infected by the experimental method.

The defense mechanism apparently depends primarily upon neuron susceptibility. True acquired active immunity requires some modifying action which results from active neural infection. This modification need not be associated with demonstrable virucidal antibodies in the blood. Such humoral antibodies as may make their appearance in naturally acquired active immunity may result from chance contact of virus with extraneural tissue and may therefore be entirely adventitious so far as true immunity is concerned. This would offer an additional explanation for the failure to prevent infection by the prophylactic injection of immune serum.

Active Immunity.—With the failure of the use of immune serum to prevent or protect, attention has been focussed on the possibility of increasing resistance through the use of a vaccine. A considerable body of knowledge relating to active immunity to the virus of poliomyelitis has grown up since the condition was first described in 1910. It was reviewed by Flexner in 1932.²⁸ Hope was kindled that a safe and effective method had been discovered by the independent publications of Brodie, and of Kolmer in 1935. These authors on the basis of rather limited observations on monkeys decided that they were justified in giving their respective methods a trial in human beings.

Brodie²⁹ used an emulsion of monkey-cord virus, treated with formalin the minimum amount of time necessary to render it non-infective for monkeys. Whether this treatment simply reduced the dose or modified the still living virus or whether it was no longer living could not be determined. Monkeys and children, injected subcutaneously with this material developed or showed an increase in neutralizing antibodies in their blood serum. As has since been pointed out, the demonstration of such substances in blood serum is not necessarily synonymous with neural immunity. Olitsky²⁹ and Schultz²⁷ independently found that monkeys vaccinated with this material and showing neutralizing antibodies in their blood serum were still susceptible to experimental infection by the intracerebral route.

A careful field trial of Brodie's vaccine was undertaken by the United States Public Health Service. Attempt was made to set up the test under carefully controlled conditions. Gilliam and Onstott³⁰ were unsuccessful in securing a sufficiently large experience to permit definite conclusions regarding the protective value of the procedure. They calculated that in an area where the control group were spared from epidemic prevalence, as were the children in the location in North Carolina and Virginia where this study was conducted, 7500 vaccinated children together with 7500 controls would have been necessary to show conclusively the value of a perfect vaccine against poliomyelitis. They were able to show, however, that Brodie's vaccine was relatively harmless, although they encountered a few very disturbing reactions.

Kolmer³¹ used a 4% "remote" monkey passage virus treated with 1% sterile solution of sodium ricinoleate. He believed that through prolonged passage in monkeys his strain of virus had undergone some reduction in virulence for man, although he was unable to prove the point. He believed that it was further attenuated by the chemical treatment with sodium ricinoleate. Although he could infect monkeys by the intracerebral inoculation of 0.3 cc. of the vaccine, he failed in 42 attempts to infect monkeys by the subcutaneous injection of 0.5 cc.

per kilo, whereas in a series of 20 attempts with similar doses of fresh untreated virus paralysis developed in 1. He interpreted his experiments as indicating that the effect of sodium ricinoleate and later of the added preservative phenyl-mercuri-nitrate was one of devitalization or attenuation. The vaccine contained, nevertheless, living virus.

Following preliminary observation on 473 individuals to whom this material was given in Philadelphia, amounts totalling 22,022 cc. were distributed through 719 physicians for immunization of over 12,000 individuals. No attempt was made to measure the degree of protection afforded under natural conditions of exposure by comparison of carefully balanced test and control groups. Poliomyelitis developed in 10 individuals who had received 1 or 2 doses. Five of these were fatal. Kolmer³¹ thought that some but not all of these were directly attributable to infection from the live virus in the vaccine.

Rivers³² pointed out that Kolmer's experiments failed to prove that the virus contained in the vaccine emulsion had been decreased in infectivity any more than could be accounted for by dilution and the subcutaneous route of administration. Both he and Leake³³ presented convincing evidence that the cases of paralysis following the use of Kolmer's vaccine were in fact due to the inoculated living virus and not to coincident natural exposure. The method was therefore condemned as unsafe.

So far it has been impossible experimentally to confer immunity upon monkeys without giving them a clinical attack of the disease with its attendant risks. Whether the human species differs in this regard is yet to be ascertained. Epidemiologic data are interpreted as indicating that a vast majority of human beings are immunized by a subclinical attack. Whether the ingenuity of experimental investigators will be sufficiently great to develop a method which will imitate nature in this regard, and hold no risk of permanent neural damage, remains to be seen. In the meantime attention has been directed to a less dangerous procedure involving an effort to strengthen the barrier at the portal of entry.

Protective Effect of Intranasally Instilled Chemicals.—Armstrong and Harrison³⁴ found that if monkeys were treated by intranasal irrigation with 4% alum solution they offered a high degree of resistance against subsequent intranasal instillation of virus emulsion. Their observations were confirmed by Sabin, Olitsky and Cox³⁵ who add that protection is also afforded by 4% tannic acid. Schultz and Gebhardt³⁶ obtained similar results with picric acid, p-nitrophenol, trinitroresol and mercurochrome. The duration of this nonspecific protection is variable but can be maintained for some time if the treatments are repeated. In a later communication Armstrong and Harrison³⁷ confirmed and extended their earlier observations to include the effect of intranasal instillations of a considerable number of chemical solutions upon infection of mice with encephalitis virus and upon infection of monkeys with poliomyelitis. They found that intranasally instilled chemicals effective in the former were also effective in the latter. This facilitates further study of this question by the use of experimental encephalitis in mice. Picric acid, 0.32% to 0.64%, either alone or combined with alum, was found superior to 4% alum and the most satisfactory and efficient agent so far tried. The protective effect from spraying the nose of monkeys with this chemical solution was apparent

against intranasally inoculated poliomyelitis for at least 4 to 7 days following its last administration. It is believed that it exerts its protective effect locally either by rendering the mucous membranes less permeable to infection or possibly by direct action on the virus, or both.

In his most recent communication Armstrong³⁸ followed the ingenious experiment of Lennette and Hudson³⁹ in which they sectioned the olfactory tract of 5 monkeys and then inoculated them intravenously together with 5 intact controls. Four of the 5 controls succumbed to poliomyelitis, while the 5 animals whose olfactory tracts were sectioned remained well. In similar manner Armstrong gave intranasal instillations of 1.5 cc. of 0.32% picric acid in saline into each nostril of 9 monkeys. These 9 prepared and 9 nontreated control monkeys were then inoculated intravenously with poliomyelitis virus. Among the picric-acid-prepared animals there were 2 deaths due to poliomyelitis, while among the nine controls there were 6 deaths from poliomyelitis. The experiment was interpreted as indicating that picric acid instilled into the nostrils tends to protect monkeys *even against intravenous inoculations* and to confirm the conclusions of Lennette and Hudson regarding the importance of the nasal membranes and olfactory tract as a portal of entry.

As far as present information goes, the instillation of such a solution of picric acid into the nostrils of a human being is a harmless procedure. Whether it will afford the protection which is evident in monkeys remains to be determined—and incidentally is a much more difficult matter to prove. Even though the protection afforded be partial and temporary, it gives hope of at least reducing the number who suffer from clinical attacks of the disease during periods of unusual (epidemic) exposure.

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ORIGINAL ARTICLES.

**PURPURA HEMORRHAGICA WITH LYMPHOCYTOSIS; AN
ACUTE TYPE AND AN INTERMITTENT
MENSTRUAL TYPE.**

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THE occurrence of thrombopenic purpura associated with a normal or increased number of white blood cells, the majority of which are other than neutrophils, suggests the diagnosis of leukemia. In idiopathic purpura hemorrhagica the neutrophils usually form over 50% of the white blood cells. The absence of leukopenia would practically rule out one or another form of aplastic or aregenerative anemia or "malignant" neutropenia. If anemia is absent, or present only in proportion to the amount of blood lost, it would make the diagnosis of leukemia unlikely, because in this disease pronounced thrombopenia and hemorrhage seldom occur except relatively late when there is a considerable degree of anemia. If then, upon studying the white blood cells, it is decided that the majority are atypical lymphocytes with none or very few grossly immature cells, one might wonder if the patient had infectious mononucleosis. In that condition, however, purpura with decreased blood platelets is very rare. Tidy¹ located only 5 cases recorded in the literature with purpura, and at least 2 were probably not examples of infectious mononucleosis.

It was this general state of affairs that was presented particularly by the first 3 acute cases I shall describe. The striking feature of the second 3 cases was the occurrence of intermittent purpura hemorrhagica associated with menstruation. In these latter cases there occurred a temporary increase of lymphocytes so that during the period of elevation the cases simulated somewhat the acute cases. All 6 cases terminated favorably.

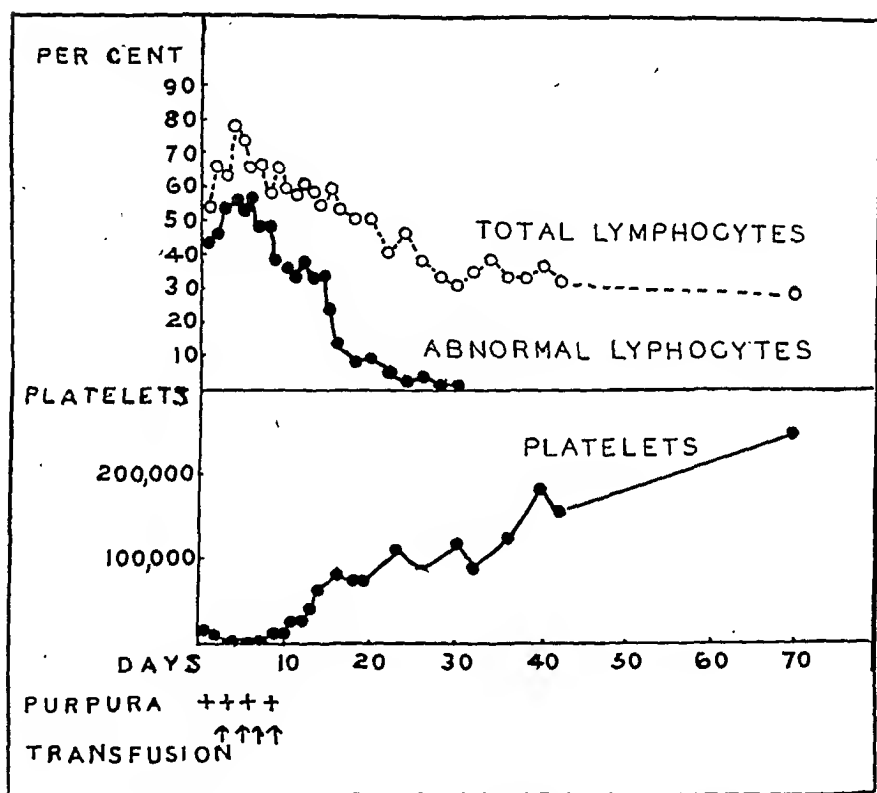


FIG. 1.—Case 1. Acute purpura hemorrhagica with lymphocytosis.

Acute Purpura Hemorrhagica With Lymphocytosis. Fig. 1 records the significant data concerning the lymphocytes and blood platelets in 1 acute case (Case 1) that are also typical for 2 others.

The cells recorded as atypical lymphocytes were similar in the 3 cases. All large lymphocytes, many of which were somewhat atypical, have been included with the atypical lymphocytes. The cells resemble the type seen in infectious mononucleosis. Intermediate sized cells predominated. Irregular shaped cells, lobed and double nuclei, abnormally deeply staining nuclei, abundant cytoplasm with atypical granules, and a considerable variation in the size of cells and nuclei were features. At times many cells

seemed distinctly young and occasionally one suggested a lymphoblast. Very bizarre cells were relatively rare. The cells in Case 2 were probably more atypical than in Cases 1 and 3, but in each instance the cell character was sufficiently peculiar to cause considerable anxiety as to whether leukemia existed or not.

In each case the monocytes were within normal limits. Basophils were absent or very rare. Eosinophils were present, usually 1 to 2% of the white blood cells. There was perhaps a tendency for them to be slightly more frequent when the platelets were low than after bleeding ceased; for example, in Case 1 they were 2.5 to 5% during the former period and not over 2.5% later on. Among the neutrophils young forms were present. The absolute number of neutrophils was never markedly reduced but tended to be slightly below normal when the lymphocytes were at or near the peak of their rise. The white cell counts varied from 6000 to 16,000 per c.mm., being greatest at the height of the lymphocytosis. The red cells showed only the features associated with rapid loss of blood; signs of active regeneration were present. Anemia did not become marked and its degree is noted with the synopsis of salient aspects of each case.

Case Reports. CASE 1.—The patient was a man, aged 21, about 15 pounds underweight for his height, who had had no serious illness. He was subject to "colds" and nasal catarrh; the latter was evident at the onset of bleeding. After feeling tired for a few days in April his gums bled and he noticed purpuric areas on his legs. Purpura rapidly appeared on many parts of his body, and bleeding from the gums and nose became marked. There was slight bleeding from the kidneys and, with the development of abdominal pain, probably hemorrhage into the intestines. Four blood transfusions were given and no hemorrhagic manifestations developed after the twelfth day. At the onset a few lymph nodes were palpable laterally on each side of the neck which, although smaller, remained palpable a week after the bleeding ceased. There was no other enlargement of lymph nodes and the spleen could not be felt. During the period of bleeding, when the platelets were very few and the lymphocytes increased (Fig. 1), the temperature varied from 98° to 100° F. The hemoglobin remained above 12 gm. per 100 cc. The white cell count fluctuated between 6000 and 12,000. As bleeding ceased, the platelets rose and lymphocytes fell. After about a month's convalescence the patient felt and appeared perfectly well, and during the subsequent 2 years showed no signs of hemorrhagic disease.

CASE 2.—Case 2 was entirely similar to Case 1. I am indebted to Dr. J. S. Lawrence for some of the data for this patient, who was a well-developed and nourished man of 23. The chart of his lymphocytes and platelets is almost identical to that for Case 1 (Fig. 1). During the period of bleeding which lasted 10 days, and when the platelets were essentially absent and the lymphocytes elevated, the white cell count varied from 8000 to 15,500, and then for a month remained close to 10,000.

The patient was in robust health until 15 days before purpura was first noticed, in September, when he experienced a mild "head cold" which lasted 4 days. He felt perfectly well during the week before purpura began. There first appeared petechiæ on his legs. Within 24 hours purpura became extreme, extending essentially all over the body, and bleeding from the gums

developed. There rapidly followed very pronounced loss of blood from the kidneys and intestinal tract, so that in the subsequent 10 days he was transfused 9 times, being given *in toto* 4330 cc. of blood. Bleeding then ceased, never to return, as the platelets rose reaching 100,000 per c.mm. in a week. They remained at about this level for a month, and at the end of the next month were about 200,000. Some further increase to normal subsequently occurred. The hemoglobin remained close to normal, chiefly owing to the donors' blood, in view of the marked amount of blood lost. A few slightly enlarged lymph nodes were at first detected in his neck but by the fifth day of bleeding they were considered normal. However, a few moderately enlarged nodes then were palpable in the axillæ, but became normal in size within a week. The spleen was thought to be palpable on the first 2 days of the illness, but was never felt thereafter. The temperature remained usually normal and always within a degree of normal except for three transient rises accountable for by transfusion. This young man has remained perfectly well in the last 3½ years and his blood has shown no abnormality.

CASE 3.—A 10-year-old, well-developed, slightly thin girl; she probably had very mild rheumatic fever at the age of 6 years, when her tonsils were removed. Having felt slightly tired for a month she suddenly developed, in October, an extensive number of purpuric lesions all over her body and severe bleeding from the nose, gums and kidneys. Transfusions of blood were given and no bleeding occurred after the twelfth day. On the third day of her illness when the platelets were virtually absent, the white blood cell count was 16,000 per c.mm., and the lymphocytes 74%, most of which were atypical. On the eighth day the lymphocytes were 64%; the white blood cells 14,000, and the platelets very low. The blood appeared normal 3 weeks after bleeding ceased. The hemoglobin fell to 60% of normal before transfusion and remained over 80% thereafter. During the height of her illness the spleen was transiently palpable at the costal margin and a few lymph nodes were palpable in her axillæ, neck and groins but none were larger than about 2 by 1 cm. The pharynx was slightly injected; thick, sticky mucus adhered to the mucous membrane; there was no discharge from her nose. The temperature remained below 100.3° F. The girl appeared normal during the following year.

In this case the sheep cell agglutinin test was negative. It was not done on the blood of the other 2 patients. In none of these 3 patients was there a history of a recognized allergic manifestation or a history of significant contact with poisons or the taking of any drugs.

SYNOPSIS OF A PREVIOUSLY REPORTED² SOMEWHAT SIMILAR CASE. An abnormally thin boy, aged 18, observed in 1921; for 2 months he had felt unusually tired and "out of sorts." Then symptoms of anemia, including shortness of breath and palpitation of the heart, developed over a period of 2 weeks, when a moderate amount of purpura appeared with relatively mild bleeding from the gums and nose and persisted for somewhat over a week. The spleen descended 5 cm. below the costal margin, and lymph nodes were obviously enlarged in the neck, axillæ and groins. There was marked chronic tonsillitis. Fever was only slight. On the fifth day of purpura the hemoglobin was "55 per cent," the platelets about 25,000 per c.mm. and the white cell count 12,000, with 81% lymphocytes nearly all of which were pathologic. Many lymphocytes were more abnormal and immature than in the 3 cases recorded above. The platelets were normal within 2 weeks after the bleeding ceased. The patient slowly improved, the tonsils were removed, and during the following 8 years he remained well.

Discussion. This case, although having much in common with the 3 preceding cases, differs from them in that anemia developed insidiously before purpura appeared, and the lymph nodes and spleen were very distinctly larger. The thrombopenic purpura lasted, however, about the same length of time. The onset with anemia does not suggest infectious mononucleosis, yet the white blood picture and enlarged lymphoid tissue is consistent with that disease, but the marked decrease of platelets is at least very atypical for the condition. Originally leukemia was suspected. In the other 3 cases the onset of illness was abrupt. The part played by the "head cold" which began 15 days before purpura appeared in Case 2 and by a possible upper respiratory tract infection in Cases 1 and 3 is interesting to speculate upon. Did some allergic-like mechanism play a rôle? The outstanding feature of each case was pronounced hemorrhage. The sudden onset of extensive purpura without anemia is at least very rare in acute leukemia or in conditions causing infiltration of the bone marrow with abnormal tissue, and the lymphocytes were not of the type seen in acute leukemia. The course taken at first by the case reported before, with anemia at the onset of illness, simulated leukemia more closely. The lymphoid tissue was less swollen than in the average case of infectious mononucleosis, being very slight in Cases 1 and 2 but distinctly more evident in the 10-year-old girl (Case 3). Fever was an inconspicuous feature, again unlike typical infectious mononucleosis, as is the negative sheep cell agglutinin test in Case 3. Usually in acute idiopathic purpura hemorrhagica the neutrophils are increased, so that the white cell picture of these cases is unlike what one expects in this condition. Shall we call these cases idiopathic purpura hemorrhagica with atypical lymphocyte reactions or atypical cases of infectious mononucleosis with pronounced thrombopenic purpura? Nosography, as Faber has pointed out, is but one means that aids our understanding. The cases illustrate, as do the 3 other cases about to be described, that severe alteration in the blood and serious symptoms can take place and yet recovery occur. I prefer to think of these cases as examples of purpura hemorrhagica with atypical white blood cell response, and this seems to be rather definitely so in the following 3 cases.

Intermittent Menstrual Purpura Hemorrhagica Complicated With Temporary Increase of Lymphocytes. The outstanding feature of the next 3 cases to be described (Cases 4, 5 and 6) was the occurrence of a rapid fall of the platelets to very low levels and the appearance of purpura in association with menstruation, followed by a quick rise of the platelets and cessation of abnormal bleeding, only to have these events recur with the next menses. In the first 2 cases close to the time of one menstrual period the lymphocytes increased and later on fell, and in the third case these cells increased

in association with 2 consecutive menstrual periods. Thus, the blood picture of these cases temporarily resembled that seen in the acute cases.

The usual case of intermittent purpura hemorrhagica, which is rarer than the chronic continuous type, exhibits two or more attacks of hemorrhagic manifestations with periods of thrombopenia at irregular intervals of weeks, months or years. There also occur cases where the platelets remain considerably decreased for years, with bleeding appearing only at varying and less often regular intervals, when there is apt to be a further temporary drop in the platelets. Such cases have also been referred to as intermittent in type. In women with this condition, purpura and bleeding from mucosæ may be prominent only at the time of the menstrual period. Sometimes excessive menstruation is so much more prominent than other bleeding that it appears as essentially the only hemorrhagic manifestation, and splenectomy may be the final procedure to give relief. Rarely in such cases lymphocytes, almost all normal in type, may reach 50%. The relationship of decrease of platelets with abnormal bleeding to menstruation appears to have received little attention. Leschke and Wittkower³ present briefly most of the scant available information. Some investigators have maintained and others have denied that normally there is some decrease of the platelets close to the onset of menstruation, with a quick rise as the normal blood loss produces a stimulus for more platelets. It is interesting to note that in Werlhof's classic acute case which recovered in about a week the onset was "towards the period of her menses" and this has been true for other such cases. One must distinguish between the occurrence of menorrhagia with the first menstruation occurring in a case of chronic thrombopenic purpura and the onset of purpura hemorrhagica with menstruation. There was nothing to suggest that in Cases 4, 5 and 6 there had been any hemorrhagic disorder before the onset of their periodic purpura hemorrhagica.

CASE 4.*—Significant data are presented in Fig. 2. The patient was a divorced woman, aged 40, 5 ft. 1 in. tall, weighing 132 pounds, who had never been pregnant. Her tonsils had been removed, a maxillary sinus opened, and cholecystectomy for stones performed more than 4 years before the present illness began. About 1 month before bleeding commenced, she had recovered from a rather prolonged attack of low-grade pharyngitis which had caused her to feel "below par."

Suddenly, while feeling perfectly well, her gums began to bleed on the day her menstrual period was due in February, 1935. Very soon she felt a stinging sensation in the skin all over her body, especially on her legs. Numerous small petechiæ were found and several ecchymoses about 5 by 7 cm. in size. Within an hour an excessive flow from the vagina began. Her periods had always been normal and regular on a 28-day cycle. She was transfused twice and abnormal bleeding ceased within 3 days. The

* I am indebted to Dr. Alvin G. Foord, of Pasadena, for the data on this case, with his kind permission to report it.

platelets (Fig. 2), which were very few, increased promptly and she soon felt perfectly well and returned to her active work as a trained nurse. Again suddenly while at work, and on the day her period was due, the same symptoms and signs rapidly developed and the menstrual flow was profound. Once more 2 blood transfusions were given and bleeding soon ceased with rapid increase of platelets. She then received 300 Roentgen ray units over her spleen in 14 days when there were essentially no symptoms. As the time for her period approached the platelets fell and she received 2 more blood transfusions. She did not develop purpura and the period which came 5 days late was probably only slightly excessive. She had no fever until the day after the last Roentgen ray treatment (4 days before her period was due). That day fever appeared and persisted for

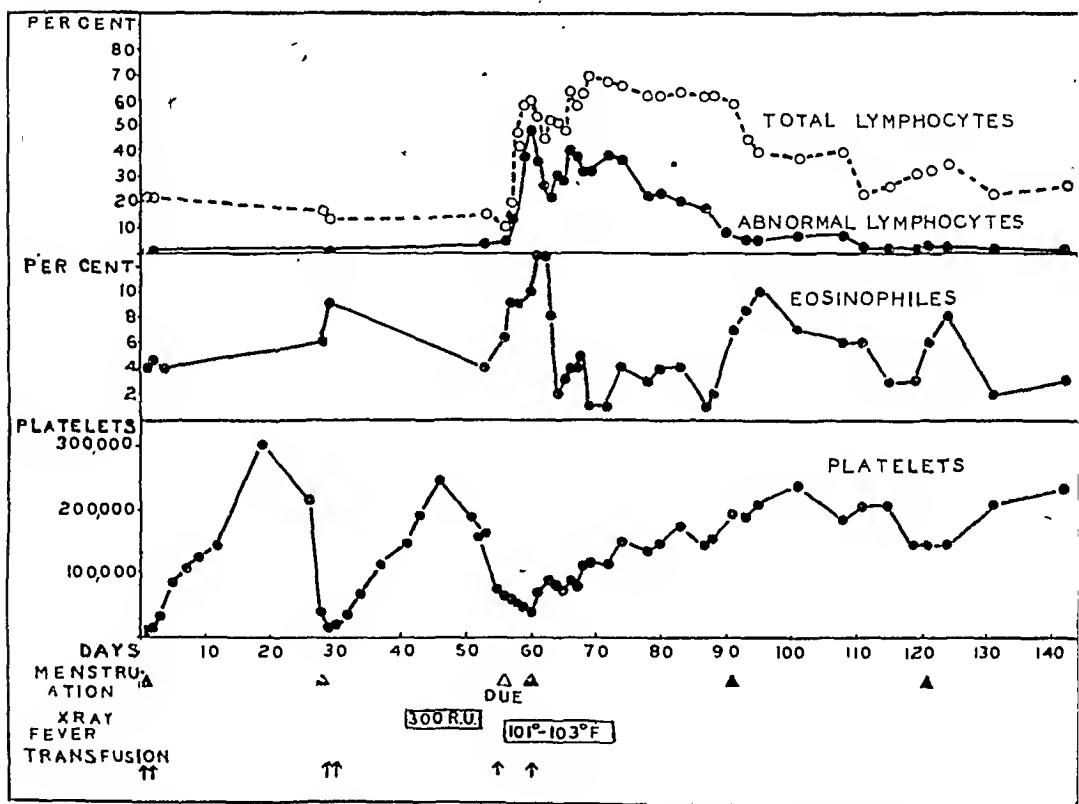


FIG. 2.—Case 4. Intermittent purpura hemorrhagica associated with menstruation. A temporary increase of lymphocytes complicates the picture.

about 20 days; the temperature varied each day from 103°, usually about 102° to 99° or 100° F., being less after about the fourteenth day. With the fever, nausea was very troublesome. Fig. 2 shows the lymphocyte response at this time. The lymphocytes appeared less abnormal than in Cases 1 and 2. At the height of the fever the sheep cell agglutinin test was negative and the same result was obtained about 10 days later. There was no enlargement of the spleen or lymph nodes at any time. The throat and nasal passages were normal. Various types of cultures and agglutination tests and all other examinations were negative, including Roentgen ray examination of the lungs.

At no time was there any noteworthy anemia. Coincident with fever and increase of lymphocytes the white blood cells remained in the vicinity

of 11,000 per c.mm., and before and after this event they were usually about 7000. The eosinophils increased temporarily in association with the menses (Fig. 2). Basophils were very rare. The monocytes were not increased. Young forms of neutrophils were increased after Roentgen ray treatment and remained somewhat elevated during the period of fever.

No evidence of any sort, which was diligently searched for, indicated that the patient had taken drugs or had been exposed to poisons. She gave no history to suggest allergy nor was there a family history of this condition.

Following a convalescent period of about 5 weeks after fever ceased; she has appeared well in the subsequent 9 months.

It seems unlikely that the Roentgen ray treatment was responsible for the attack of fever and increase of lymphocytes, and particularly when the next case to be described which received no such therapy developed the same syndrome. The course taken by the eosinophils will be commented upon after describing the other 2 similar cases.

CASE 5.—This patient, seen 12 years ago, was an unmarried woman, aged 28, whose past history appears to have no bearing on the present illness. She was apparently well when bleeding began but had had a "head cold" about 6 weeks previously. The data for the blood are less complete than in Case 1, but the sequence of events was very similar. She had 2 mild and brief attacks of purpura and menorrhagia at the time of 2 consecutive menstrual periods, followed by much more severe attacks, of only a few days' duration, with the next 2 periods. With the subsequent period there were a few petechiæ on her legs and only slight excess menstrual flow. With each of the latter 3 attacks it is known that the platelets were very few and that they were approximately normal at some time between attacks. As the last attack was subsiding, the lymphocytes rose from about 25 to 63% when the majority were slightly abnormal in type. The white cells were about 14,000 when the lymphocytes remained elevated for about 12 days. During the first 7 of these 12 days the patient had slight fever; the temperature remained about 100.5° F. The white cell count, both before and after the temporary increase of lymphocytes, was about 7000 when the differential white cell count was essentially normal. The eosinophils were 1 to 4%, with perhaps a tendency to be more frequent near the time of menstruation. Anemia was never more than slight, in part prevented by blood transfusions at the time of the severer bleeding episodes.

There was no evidence of respiratory or urinary tract infection, and the lymph nodes and spleen remained normal in size. She gave no history of an allergic condition. It is unknown whether she had taken any drugs.

With the 2 menstrual periods following the rise of lymphocytes there were a very few petechiæ on the legs and the flow from the vagina was slightly excessive. In the next 2 years she had no hemorrhagic manifestations.

CASE 6.—The patient was an unmarried, large-framed woman, aged 26, weighing 160 pounds. The past history was essentially negative except for the fact that she had had, although not for 2 years, a few mild and brief attacks of urticaria due to no recognized cause. There was no history of other conditions suggesting allergy and no history to indicate sensitivity to any known substance.

She had a brief and mild attack of purpura 18 days before the chart (Fig. 3) commences, with somewhat excessive menstrual flow. A blood smear at this time showed the platelets diminished, the lymphocytes 30%, and the eosinophils 5%. Eight days before the next menstrual period she developed a sore throat, and 2 or 3 days before menstruation her pharynx was injected, the tonsils reddened, and fever developed.

The course taken by the lymphocytes and their relationship to the fever is shown in Fig. 3. The abnormal ones were chiefly intermediate in type and relatively slightly abnormal. At no time did the white cell count fall below 6000 or reach above 12,000, the higher counts being recorded when the lymphocytes were elevated. The periodic rhythm of the eosinophils is shown in Fig. 3. The monocytes were 3 to 8%, and the remaining cells were neutrophils. The sheep cell agglutinins were not examined.

The temperature remained elevated for 2 weeks, usually about 100.5°F ., rarely 102.5°F ., and subsided gradually. During the period of lymphocytosis there were moderately enlarged lymph nodes at the angles of the

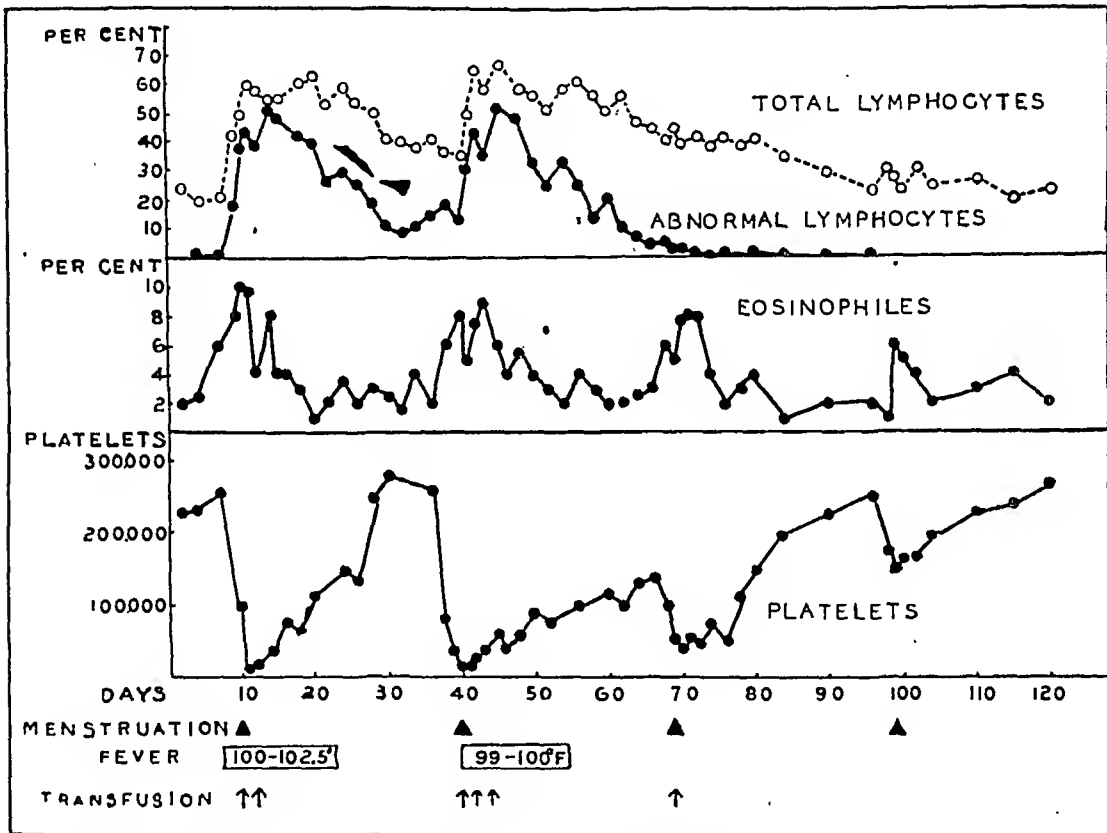


Fig. 3.—Case 6. Intermittent purpura hemorrhagica associated with menstruation. A mild attack of purpura with thrombopenia occurred with menstruation beginning 18 days before the first charted observation.

jaws and in the anterior chains of the neck. No other nodes were abnormally enlarged nor was the spleen palpable. The tonsillitis and pharyngitis remained mild and subsided with the fever; at the same time the lymph nodes receded. After fever had been absent for about 2 weeks and on the day the next menstruation began, the lymphocytes increased once more, the nodes in the neck became more swollen but less so than before, and for the following 15 days the patient had slight fever, the temperature varying from 99° to 100°F . During this time the pharynx and tonsils appeared moderately injected.

With the 2 menstrual periods that occurred when fever was present, ecchymoses and petechiae appeared especially on the legs, with marked

menorrhagia and slight bleeding from the gums and nose. After blood transfusions, abnormal bleeding ceased within 2 to 4 days. Anemia did not become pronounced. The platelets rose less and more slowly after the second of these two episodes (Fig. 3), but fell equally rapidly just before each of these 2 menstrual periods. At the time of the subsequent period the platelets fell but not to such a low level as formerly; coincident with this only very slight purpura occurred and the menstrual flow was only moderately in excess of normal. Following that period she remained well in the next 2 months, then left this country and has not been heard from.

Discussion. The association of abnormal bleeding and thrombopenia with the menses in these 3 patients suggests some altered endocrine function. If, as some investigators believe, there is normally a drop of the platelets just before menstruation, a great exaggeration of the mechanism causing this might be responsible for the development of purpura. Increased capillary permeability has been shown to occur at the time of menstruation and ovarian dysfunction has been considered a cause of some hemorrhagic conditions. Cases of intermittent purpura hemorrhagica differ distinctly from such cases of hemorrhagic diathesis as described by David,⁴ and supposed to be due to altered ovarian function. In those cases the platelets are not reduced. The condition of easy bruising, which is sometimes aggravated at the time of menstruation, especially as the menopause approaches, is also, of course, a separate disorder.

The course taken in Cases 4 and 6 by the eosinophils with their increase at about the time of menstruation and decline thereafter, only to rise again in association with the next period, is rather fascinating to speculate upon. It suggests some endocrine rhythm or allergic mechanism. Eosinophilia occasionally develops from altered endocrine functions and may occur with suppression of anterior pituitary function.⁵ The recurrent urticaria that had existed in Case 6 was the only symptom evidenced by any of the 3 patients to suggest an allergic background. Is it possible that the first 2 patients developed some allergic state owing to the upper respiratory infection they had had about a month before purpura appeared? The only infection the third patient is known to have had within months of the time purpura developed was after the first attack of bleeding. Purpura hemorrhagica may be induced in animals by antiplatelet serum and may develop in man as the result of "sensitivity" to certain drugs such as "sedormid" (allyl-isopropyl-acetylurea) and quinin. Various forms of eruptions, not only especially erythema and urticaria, but also ecchymoses and purpura without reduction of platelets occurring periodically with, or in place of, menstruation, have also been thought to be sometimes allergic in nature.⁶ Some such cases of vicarious menstruation probably are associated with low blood platelets and, although an allergic mechanism may be operative, the conception of altered endocrine function seems

equally plausible. However this may be, the mechanism causing these conditions remains unknown. The reason for the cessation of the condition in the 3 cases described is as mysterious as the mechanism that initiated the difficulty.

The occurrence of lymphocytosis does not necessarily accompany this type of intermittent purpura hemorrhagica associated with the menses. The lymphocytes were never found to be over about 35% in a case of this sort described to me by the late Dr. Ralph C. Larrabee, where the attacks of purpura recurred for many months, though the ultimate outcome is unknown. I am indebted to Drs. James H. Méans and Alfred Kranes for describing to me a case comparable to the 3 described above, in which there was no evidence of increase of lymphocytes or eosinophils. This patient, after many recurrent attacks of purpura associated with menstruation, had none for about a year when they returned.

The cause of the lymphocyte increase in the 3 cases described remains unsolved. The absence of other signs of infectious mononucleosis in Cases 4 and 5 than fever, the blood picture, and the negative sheep cell agglutinin test in Case 4, make it unlikely that both these patients developed this disease in addition to intermittent thrombopenia. In Case 6, which seems unique, the occurrence of throat infection directly before and during the first lymphocyte reaction and apparently present with the second temporary increase of lymphocytes would seem to be in some way responsible for the white blood cell picture. The occurrence of adenopathy with increase of lymphocytes is not rare with infection independent of infectious mononucleosis. The presence of fever with each of the lymphocyte reactions in the 3 patients certainly suggests infection in spite of no local signs of infection in Cases 4 and 5. Even if infection was chiefly responsible for the lymphocytosis, one is led to wonder if altered endocrine function or allergy did not play some rôle in allowing the atypical blood response. In the acute cases with single attacks of bleeding fever was conspicuous by its minor degree or absence, and it occurred only during the time of bleeding. In the intermittent cases fever continued long after bleeding ceased. Another contrast between the lymphocyte responses in these two types of cases is that the abnormal lymphocytes in the acute cases decreased in close association with cessation of hemorrhage, while in the intermittent cases they fell a considerable time after an attack of purpura. It would seem as if more than one cause and mechanism for the lymphocyte responses was operative in the 6 cases, but speculations accomplish no very useful object.

Though significant information is here necessarily limited to simple description, we must always remember that our final aim should be to acquire knowledge of the etiology and pathogenesis of morbid processes, so as to be able to apply proper corrective and preventive measures.

Summary. A description is given of: 1. Three non-fatal cases of acute purpura hemorrhagica (thrombopenic purpura) with pronounced increase of lymphocytes, many of which were abnormal.

2. Three cases of purpura hemorrhagica occurring periodically with menstruation which after from 3 to 7 attacks ceased spontaneously. In association with 1 attack in 2 cases and 2 attacks in the third case a temporary increase of lymphocytes occurred associated with fever.

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QUANTITATIVE VARIATIONS IN THE HEMACYTOLOGIC CONSTITUTION OF HEALTHY MEN AND RABBITS.

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For the past several years this laboratory has been conducting a systematic survey of the genetic constitution of the rabbit, particularly with reference to breed characteristics and hereditary abnormalities. Several methods have been utilized for the quantitative assay of genetic constitution, one of these being the numerical estimation of the various formed elements of the blood. By employing precise technical procedures, and the biometric method of group analysis, numerical constants for each of the blood cells have been defined for the healthy rabbit. Moreover, the reactivity of the animal host, upon receiving the impact of disease, or when subjected to physiologic or environmental stresses, has been studied in terms of the reflected numerical alterations in the blood cytology.

In this and previous reports the term hemacytologic constitution is used to designate the composite blood formula for the individual, race or family. This entity, in conjunction with many others, comprises the summation known as constitution. In a previous com-

munication¹ it was shown that the blood cytology of healthy rabbits of the same breed was more alike than the blood cytology of individuals of different breeds, and that a characteristic and typical blood formula existed for each variety of standard breed of rabbit studied. Since all known variables had been held constant during this investigation, it was concluded that the differences in the blood cytology of different breeds were largely inherited differences. This study it should be noted, was concerned with the hemacytologic constitution of *races* or *breeds* of rabbits. In the present report observations are presented with reference to the hemacytologic constitution of *individuals*; it will be shown that characteristic and typical blood formulæ exist for each of several healthy individuals representing the two species of rabbit and man.

The present report so far as we know offers the only biometric evidence to justify this concept, which, however, has been expressed in more or less similar form by previous investigators. Miller² stated that the interpretation of any differential count should be based on a knowledge of that particular person's normal blood picture when possible, on the average values for the locality in which the individual resides, and a consideration of those factors peculiar to the individual which modify that particular blood. Doan and Zerfas,³ noting that the red and white cells probably change their relative concentrations in the blood from time to time, advocated a zonal concept with adequate individual extremes. Smith and McDowell⁴ studied the normal rhythm of the white blood cells in two women subjects, and concluded that the number of white cells varies within certain limits, these limits being different in different persons, and under normal conditions constant in the same person. According to Medlar⁵ the greatest value of the leukocytic formula in pathologic states is when the normal leukocytic formula for the individual has previously been established. Shaw⁶ concluded that the number of leukocytes is a character of the individual, since the range of variation of the total leukocytes in the year is the same as in one person in 24 hours, but less than in a population. With this conclusion Garrey and Bryan⁷ appear to agree.

Material and Methods. The plan of the experiment was as follows: Weekly or biweekly complete blood examinations were made on a group of 6 healthy rabbits and 5 healthy young men. The rabbits were examined over a period of 2 years, the men for 1 year. The mean values for each of the blood cell elements of each individual were then calculated from these repeated observations, and a comparison of the individuals in each group with regard to these mean values was made.

Rabbit Material. When the investigation was begun in the fall of 1930, 10 rabbits comprised the group, but during the ensuing 2 years of observation 4 of them died from intercurrent infection. The available observations on these 4 animals are not included in the analysis. The rabbits were all males of the usual brown-gray hybrid variety, and were approximately 6 to 8 months of age at the beginning of the experiment. Throughout the

observation period they were housed in well-ventilated, well-illuminated rooms. The diet consisted of hay, alfalfa, a commercial food pellet of compressed grains, and a free supply of water.

Human Material. The selection of the young men whose blood cytology is here reported was influenced only by the chance circumstance that they were all active in the same laboratory at the time of the investigation. All had been living in the northeastern part of the country for a minimum period of 5 years, but one or two had made more or less extended trips South and North during this period. The diet was of the usual American type, with slight variations governed by individual predilection. A thorough physical examination was not performed at the beginning or during the observation period; the young men are designated as "healthy" because of their regular attendance in the laboratory and their symptom-free state throughout the study.

Number of Observations. A weekly complete blood examination was conducted on each of the 6 rabbits during the academic year beginning October 30, 1930, and ending June 18, 1931, with 1 examination on June 11 omitted. During the following year biweekly counts were made beginning October 15, 1931, and ending June 23, 1932. Thus during the interval from October 30, 1930, to June 23, 1932, each animal in the group had 51 complete blood examinations,* each made during the period from 9 A.M. to 1 P.M. on the same day of different weeks.

Parallel and similar blood examinations were conducted on the 5 human subjects during the year beginning October 31, 1931, and ending June 23, 1932, with 18 biweekly counts on each individual.

Blood Counting Technique. The pipettes employed were all certified for accuracy by the United States Bureau of Standards. The supravital neutral red technique for differential counting was followed throughout. Platelet counts were made by the method of Casey and Helmer,⁸ and hemoglobin estimations with a Newcomber hemoglobinometer. From October, 1930, to June, 1931, each examination consisted of a differential count of 100 cells, a single red cell, white cell and platelet count, and a hemoglobin estimation based on one tube. During the second year, the examinations comprised a differential count of 200 cells, each observer counting 100 cells on different preparations, a red cell and platelet count based on the average finding in the fourth and fifth drops from a single pipette, a white cell count which was the average of the values obtained from the fourth drop from each of 2 pipettes, and a hemoglobin estimation found by averaging the determinations in each of 2 tubes.

During the second year the examinations on both rabbits and men were conducted on the same day of the week and at the same time of the day. The purpose of this procedure was to determine whether the blood cytology of the two species had correlated trends. A preliminary survey has indicated that statistically significant trends for certain blood cells do exist, but this phase of the investigation will not be considered in the present communication. The same two individuals conducted the differential counting examinations, and a single observer made all of the red cell, white cell, and platelet counts and hemoglobin estimations throughout.

Statistical Methods. The successive findings on each of the 5 young men and 6 rabbits were tabulated, and the following statistical constants were determined for each cell factor of each individual: minimum, maximum, mean, standard deviation and standard error of the mean. The mean is the arithmetic average of all observations on one variate. The standard deviation is the measure of scatter of the individual values about the mean;

* Five platelet counts and 6 hemoglobin estimations on each animal were lost.

99% of the observations will lie between the limits of the mean plus and minus two and one-half times the standard deviation. The standard error of the mean is a measure of the range of scatter of similarly obtained means; 99% of similarly obtained means are expected to fall within the limits described by the mean plus and minus two and one-half times its standard error. In all statistical procedures significance has been attached to values of $P \leq 0.01$; that is, when the probability (P) of an event occurring by chance alone was equal to or less than 1 in 100, the result was considered significant. Similarly, when the probability of an event occurring by random sampling was between 1 and 5 in 100, the result was considered probably significant ($P = 0.01 +$ to 0.05).

In order to determine whether or not significant heterogeneity existed among individuals as regards any single blood element, the method of analysis of variance as modified by Snedecor⁹ was employed. The term "variance" is used to denote the square of the standard deviation, that is σ^2 . The value "F," calculated for each blood cell element of the two groups, represents the ratio of the larger to the smaller variance. Where the variance between individuals is greater than the variance within individuals, "F" in the text-figures is preceded by a plus sign; in the converse instance, "F" is preceded by a minus sign. In the case of the rabbits, when the value for "+F" exceeds 3.08, significant heterogeneity among individuals has been demonstrated, and probably significant heterogeneity when "+F" falls between 2.25 and 3.08. These values represent significance and probable significance when there are 5 degrees of freedom for the greater mean square and 300 degrees of freedom for the lesser mean square. For the men, "+F" must exceed 3.55 to indicate significant heterogeneity, or must lie between 2.48 and 3.55 to indicate probably significant heterogeneity. In this case, these are the values representing significant and probably significant heterogeneity among individuals when the degrees of freedom of the greater mean square is 4 and of the lesser mean square 85. The interested reader is referred to the monograph by Snedecor⁹ and the text by Fisher¹⁰ for more detailed information concerning the method of analysis of variance. It should be stated that if heterogeneity among the class means has been demonstrated, then each class is theoretically a sample from a homogeneous population.

The method which has been employed for the graphic presentation of the results has been described in detail elsewhere.¹¹ The horizontal broken lines in each diagram mark off intervals on the ordinate which are equal to the estimated standard error of the difference between any two means. In all cases this value was obtained by the formula $\sqrt{\frac{2V}{n}}$ * where V represents the "within classes" variance and n the number of observations in any class. This value, although an approximation of the true standard error of the difference between any two means, is sufficiently accurate for graphic purposes. In each instance a test of its accuracy was made by obtaining the average standard error of the several means, and deriving the estimated standard error of the difference between two means by finding the square root of twice the square of this average value.

* Derived as follows:

$$\begin{aligned}
 1. \sigma \text{ mean} &= \frac{\sigma}{\sqrt{n}}. & 2. \sigma \text{ difference} &= \sqrt{\left(\frac{\sigma}{\sqrt{n}}\right)^2 + \left(\frac{\sigma}{\sqrt{n}}\right)^2} = \sqrt{\frac{2\sigma^2}{n}} \\
 3. \sigma^2 &= V. & 4. \therefore \sigma \text{ difference} &= \sqrt{\frac{2V}{n}}
 \end{aligned}$$

RESULTS. The results are presented in a series of tables and text-figures. Table 1 gives the following biometrical constants for each of the 14 blood elements of each of the 5 men: maximum, minimum, mean, standard deviation and standard error of the mean. Table 2 summarizes the values obtained by the method of analysis of variance. Tables 3 and 4 present similar data calculated from the observations on the 6 rabbits.

TABLE 1.—THE BLOOD CYTOLOGY OF 5 HEALTHY MEN.

Cell.	Individual.	Maximum.	Minimum.	Mean.	σ	σ mean.
R	A	4720	3780	4293	269	63
	B	5480	4180	4773	402	95
	C	5490	3960	4743	505	119
	D	5560	3980	4653	438	103
	E	5620	4040	4744	430	101
H	A	84.6	55.6	70.9	6.6	1.6
	B	85.9	59.7	72.3	6.6	1.6
	C	81.2	61.2	72.9	5.6	1.3
	D	86.2	62.8	74.5	7.3	1.7
	E	87.3	58.4	74.5	7.6	1.8
P	A	442	264	341	54	13
	B	582	259	371	87	20
	C	435	249	335	49	12
	D	412	243	340	46	11
	E	585	280	391	82	19
W	A	8580	5480	7036	896	214
	B	7730	4980	6383	748	176
	C	8030	4880	6212	784	185
	D	8130	4150	6128	1033	244
	E	8000	4500	5779	921	217
N	A	5472	3299	4551	649	153
	B	4263	2500	3075	483	114
	C	5240	2985	4207	623	147
	D	5647	2387	3802	907	214
	E	5360	2419	3632	712	168
N%	A	71.5	57.5	64.5	3.7	0.9
	B	58.0	35.0	48.9	5.5	1.3
	C	80.5	60.0	67.4	4.9	1.2
	D	69.5	43.5	59.3	7.2	1.7
	E	72.5	53.5	62.5	5.9	1.2
B	A	80	0	31	23	6
	B	132	32	81	31	7
	C	99	0	25	26	6
	D	90	0	46	30	7
	E	96	23	60	24	6
B%	A	1.5	0	0.6	0.52	0.12
	B	1.8	0.5	1.3	0.47	0.11
	C	1.8	0	0.4	0.45	0.11
	D	2.0	0	0.8	0.55	0.13
	E	1.8	0.5	1.0	0.40	0.09
E	A	179	0	91	43	10
	B	946	274	662	164	39
	C	233	0	113	57	13
	D	326	34	184	68	16
	E	676	0	433	159	38

TABLE 1.—THE BLOOD CYTOLOGY OF 5 HEALTHY MEN—(Continued).

Cell.	Individual.	Maximum.	Minimum.	Mean.	σ	σ mean.
E%	A	2.3	0	1.4	0.6	0.13
	B	17.3	4.3	10.5	3.1	0.74
	C	4.3	0	1.9	1.0	0.23
	D	4.5	0.5	3.0	0.6	0.15
	E	10.8	0	7.2	2.8	0.65
L	A	2092	905	1490	306	72
	B	2936	1269	1763	412	97
	C	3254	780	1349	524	124
	D	2152	977	1552	338	80
	E	1732	737	1086	259	61
L%	A	25.8	12.3	21.3	4.1	1.0
	B	33.8	21.5	27.4	4.5	1.1
	C	26.0	13.0	20.2	3.3	0.8
	D	36.0	15.8	25.6	4.3	1.3
	E	26.8	13.5	18.9	3.7	0.9
M	A	1383	595	856	199	47
	B	1072	560	781	143	34
	C	1058	102	654	193	46
	D	987	387	681	178	42
	E	860	350	608	162	38
M%	A	18.3	8.5	12.2	2.3	0.6
	B	17.0	8.5	12.3	2.1	0.5
	C	14.5	1.8	10.4	2.6	0.6
	D	16.5	5.8	11.1	2.9	0.7
	E	13.3	6.5	10.6	2.4	0.6

In this and the subsequent tables, the following symbols have been employed: R, red blood cell count in thousands; H, hemoglobin in per cent; P, platelet count in thousands; W, total white cell count; N, absolute neutrophil count; B, absolute basophil count; E, absolute eosinophil count; L, absolute lymphocyte count; M, absolute monocyte count; N%, relative neutrophil count; B%, relative basophil count; E%, relative eosinophil count; L%, relative lymphocyte count; M%, relative monocyte count.

TABLE 2.—THE BLOOD CYTOLOGY OF 5 HEALTHY MEN. ANALYSIS OF VARIANCE.

Cell.	Variance.		σ	σ mean.	σ difference.	F.	P.
	Between classes.	Within classes.					
R	717580	169260	411.0	97.0	137.0	+4.24	<0.01
H	43.3	46.0	6.8	1.6	2.2	-1.06	>0.05
P	10900	4314	66.0	15.5	21.9	+2.53	<0.05
W	3856370	784320	885.0	209.0	295.0	+4.91	<0.01
N	5555650	475750	690.0	163.0	230.0	+11.68	<0.01
N%	886	41	6.4	1.5	2.1	+21.60	<0.01
B	8914	710	26.6	6.3	8.9	+12.56	<0.01
B%	2.09	0.23	0.48	0.11	0.16	+9.10	<0.01
E	1050113	11970	109.0	26.0	36.0	+87.70	<0.01
E%	268.6	2.9	1.7	0.39	0.56	+94.20	<0.01
L	1110600	142200	377.0	89.0	126.0	+7.81	<0.01
L%	229.6	17.9	4.2	0.99	1.40	+12.81	<0.01
M	205890	31020	176.0	42.0	59.0	+6.64	<0.01
M%	13.9	5.9	2.4	0.6	0.8	+2.36	>0.05

There were four degrees of freedom for the between classes variance, and 85 degrees of freedom for the within classes variance. σ is the square root of the within classes

variance. σ mean = $\sqrt{\frac{\sigma}{n}}$, n being the number of observations, 18, in each class.

σ difference = $\sqrt{\frac{2V}{n}}$. F is the ratio of the larger to the smaller variance. P represents the degree of significance of F .

TABLE 3.—THE BLOOD CYTOLOGY OF 6 HEALTHY RABBITS.

Cell.	Individual.	Maximum.	Minimum.	Mean.	σ	σ mean.
R	1	6690	4620	5698	484	68
	2	6310	4310	5292	426	60
	3	6200	3970	5119	478	68
	4	6800	3990	5302	737	104
	5	6090	3530	4901	481	68
	6	6190	3890	5004	572	81
H	1	80.5	43.3	63.6	10.1	1.5
	2	76.7	48.7	62.6	7.2	1.1
	3	74.0	44.0	59.3	8.4	1.3
	4	80.7	48.0	62.7	7.0	1.0
	5	69.5	45.0	58.5	7.5	1.1
	6	68.3	44.0	57.0	7.7	1.2
P	1	807	280	503	110	16
	2	887	300	518	121	18
	3	1107	267	520	130	19
	4	687	287	522	119	18
	5	967	304	480	125	19
	6	823	374	556	117	17
W	1	14700	5350	8957	2729	382
	2	12300	5050	7553	1376	193
	3	17850	5800	9665	2289	321
	4	9950	4700	6651	1305	183
	5	10450	5800	7818	1052	147
	6	11800	5450	7881	1340	188
N	1	8379	1712	4223	1160	162
	2	8364	1890	3897	1216	170
	3	10545	1989	4821	1633	229
	4	6156	1718	3174	1056	148
	5	5191	1769	3503	827	115
	6	7906	1600	3559	1166	163
N%	1	68.0	32.0	46.2	7.9	1.1
	2	68.8	27.0	51.1	9.6	1.3
	3	74.0	26.0	50.2	9.6	1.4
	4	72.0	28.0	47.5	8.8	1.2
	5	66.5	25.0	44.8	9.0	1.3
	6	67.0	16.0	45.0	10.8	1.5
B	1	1741	223	808	284	40
	2	1027	98	440	222	31
	3	2534	70	761	399	56
	4	1632	200	612	262	37
	5	1141	148	551	237	33
	6	1388	92	580	261	37
B%	1	20.3	2.0	9.3	3.4	0.5
	2	12.8	1.0	5.8	2.9	0.4
	3	28.0	1.0	8.4	4.7	0.7
	4	17.0	2.5	9.2	3.3	0.5
	5	16.0	1.0	7.1	3.1	0.4
	6	15.0	1.0	7.5	3.3	0.5
E	1	384	0	143	91	13
	2	748	0	152	130	18
	3	1199	0	254	218	31
	4	384	0	139	92	13
	5	523	0	141	122	17
	6	326	0	75	65	9

TABLE 3.—THE BLOOD CYTOLOGY OF 6 HEALTHY RABBITS—(Continued).

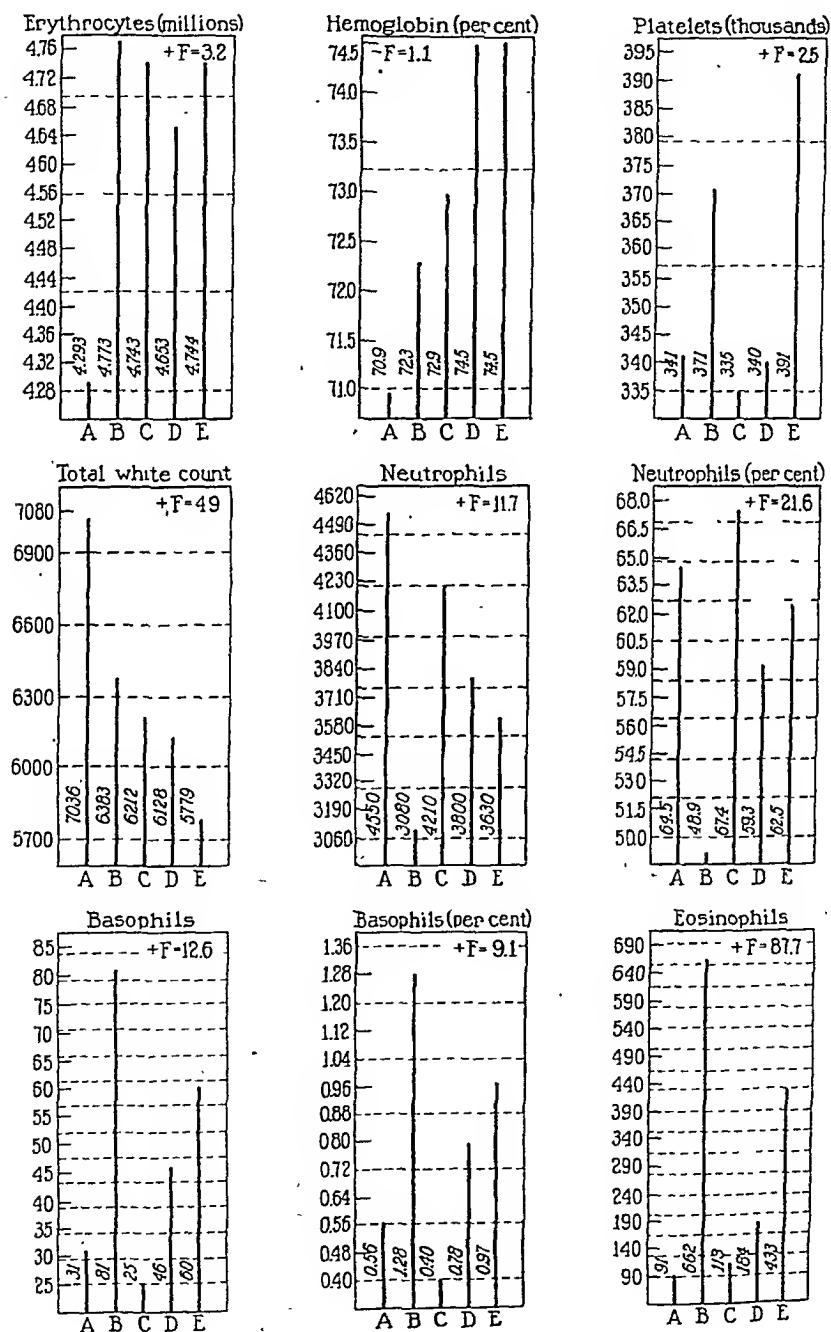
Cell.	Indi- vidual.	Maximum.	Minimum.	Mean.	σ	σ mean.
E%	1	4.0	0	1.72	1.10	0.15
	2	8.0	0	2.01	1.43	0.20
	3	11.0	0	2.74	1.89	0.26
	4	5.0	0	2.27	1.37	0.19
	5	8.0	0	1.80	1.57	0.22
	6	4.5	0	1.03	0.88	0.11
L	1	5709	1245	3204	995	139
	2	4472	1320	2524	688	96
	3	7448	1080	3188	1398	196
	4	3791	1089	2186	633	88
	5	6552	1184	3145	879	123
	6	6400	1632	3175	1019	143
L%	1	52.0	15.0	35.2	7.9	1.1
	2	56.0	18.0	33.9	9.1	1.3
	3	56.0	12.0	33.0	10.6	1.5
	4	59.0	14.8	33.0	10.1	1.4
	5	63.0	16.0	40.2	9.2	1.3
	6	65.5	21.0	40.5	11.7	1.6
M	1	1743	145	722	321	45
	2	1353	192	549	231	32
	3	1772	152	609	324	45
	4	1319	0	566	266	37
	5	1392	68	471	253	35
	6	1064	60	493	249	35
M%	1	14.0	3.0	7.7	2.7	0.4
	2	13.0	3.0	7.2	2.2	0.3
	3	14.0	2.0	6.1	2.5	0.4
	4	17.0	0	8.5	3.4	0.5
	5	16.0	1.0	6.0	2.7	0.4
	6	14.0	1.8	6.3	2.6	0.4

TABLE 4.—THE BLOOD CYTOLOGY OF 6 HEALTHY RABBITS. ANALYSIS OF VARIANCE.

Cell.	Variance.		σ	σ mean.	σ difference.	F.	P.
	Between classes.	Within classes.					
R . . .	3979500	297300	545.0	77.0	109.0	+13.38	<0.01
H . . .	331.5	66.3	8.1	1.2	1.7	+5.00	<0.01
P . . .	28945	13845	118.0	17.5	24.8	+2.09	>0.05
W . . .	58236500	3261700	1806.0	253.0	358.0	+17.85	<0.01
N . . .	17818357	1470083	1213.0	170.0	240.0	+12.12	<0.01
N%	450	88	9.4	1.3	1.9	+5.10	<0.01
B . . .	957738	81890	286.0	40.0	57.0	+11.70	<0.01
B%	96.4	12.8	3.6	0.5	0.7	+7.52	<0.01
E . . .	171300	17057	131.0	18.0	26.0	+10.04	<0.01
E%	16.8	2.0	1.4	0.2	0.3	+8.28	<0.01
L . . .	9818800	957400	978.0	137.0	194.0	+10.26	<0.01
L%	616.7	98.6	9.9	1.4	2.0	+6.25	<0.01
M . . .	417100	77900	279.0	39.0	55.0	+5.35	<0.01
M%	52.3	7.4	2.7	0.4	0.5	+7.05	<0.01

There were five degrees of freedom for the between classes variance, and 300 degrees of freedom for the within classes variance. σ is the square root of the within classes variance. σ mean = $\sqrt{\frac{\sigma}{n}}$, n being the number of observations, 51, in each class. σ difference = $\sqrt{\frac{2V}{n}}$. F is the ratio of the larger to the smaller variance. P represents the degree of significance of F .

The bar diagrams (Text-Fig. 1 and 2) illustrate graphically the significance of the difference between the represented means. The horizontal broken lines block off intervals on the ordinate equal



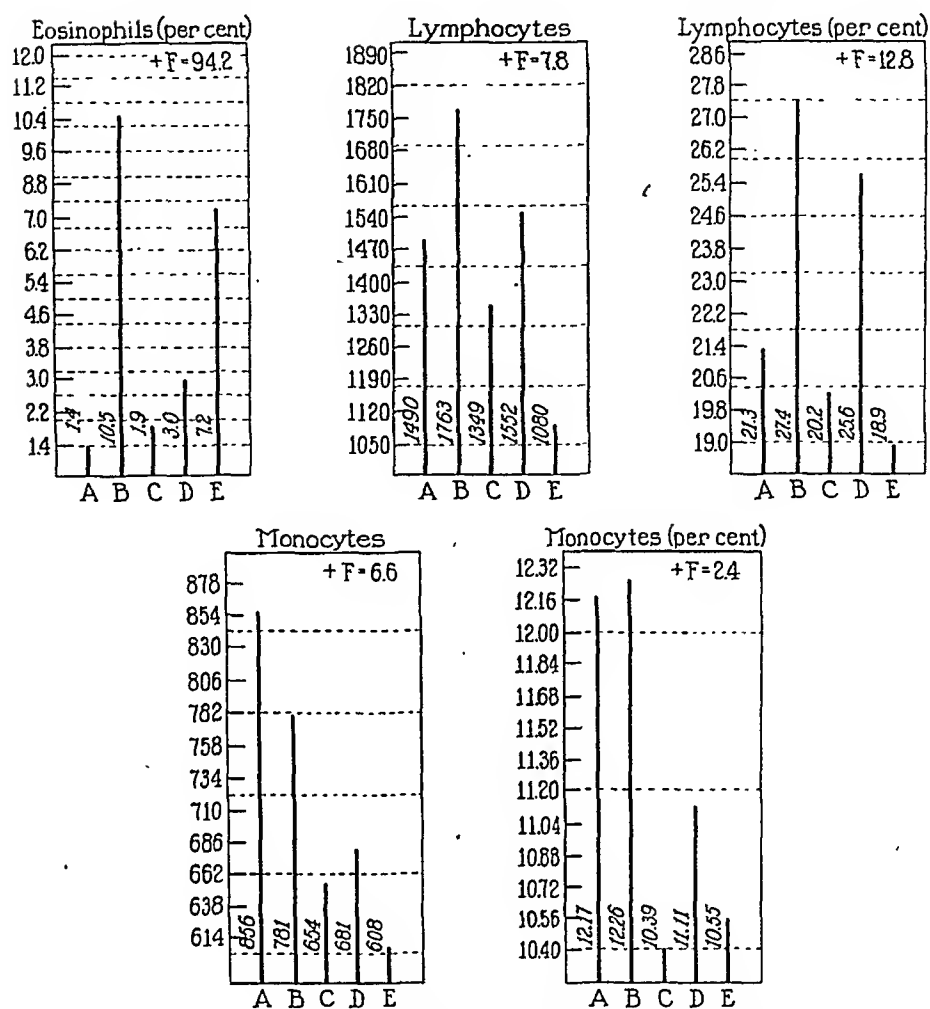
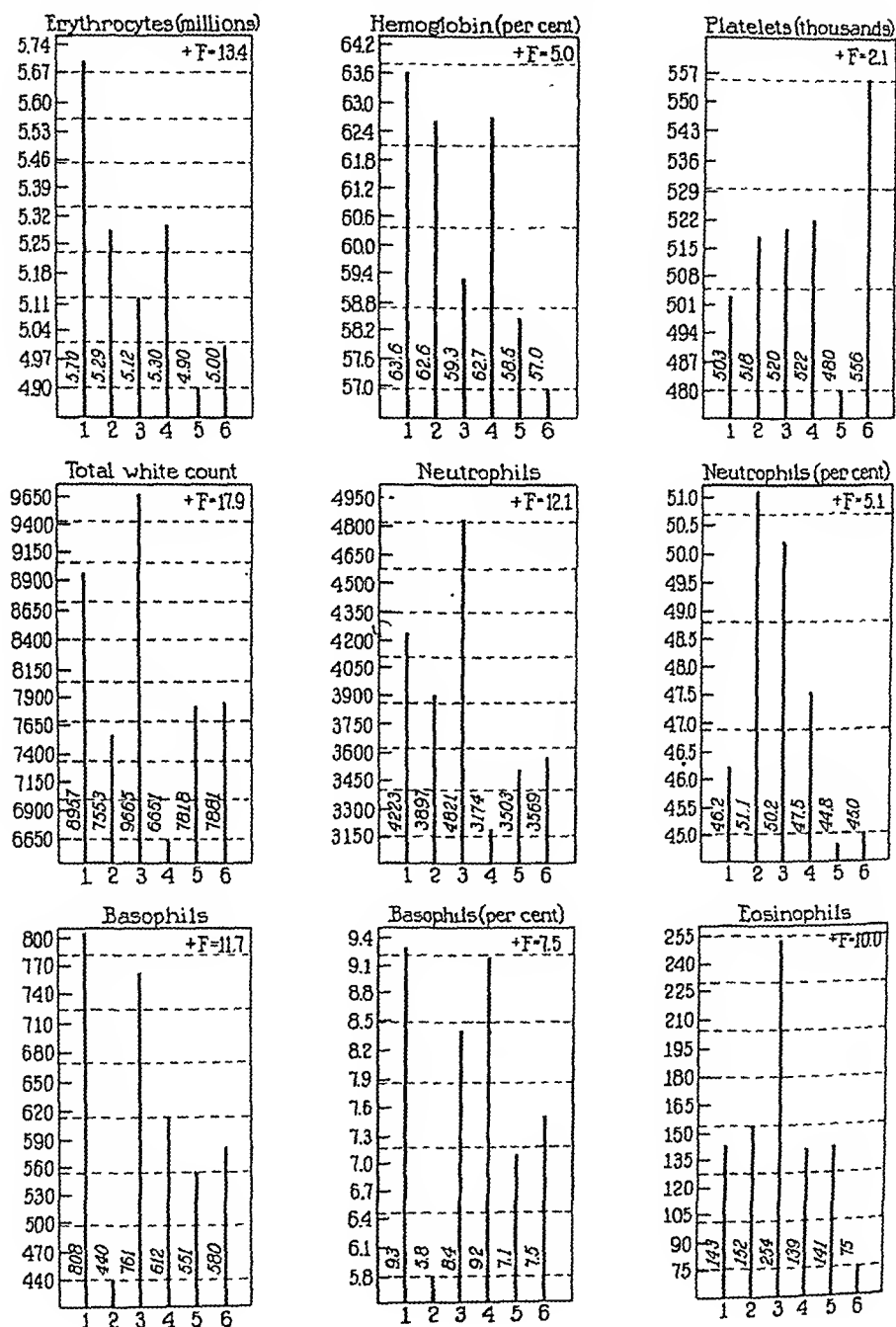


FIG. 1.—Quantitative variations in the blood cytology of healthy men. See text for explanation of horizontal broken lines and significance of "F." A, B, C, D and E represent different individuals.

to the estimated standard error of the difference between any two means. This value was derived as explained above. When the heights of any two vertical bars are separated by at least two and a half intervals, then the populations illustrated are significantly different. For example in the bar diagram headed "Erythrocytes" in Text-Fig. 1, "A" is significantly less than "B," "C," "D," and "E," since it is separated from each of these by more than two and a half intervals. "B" is not significantly different from "C" or "D" or "E," "C" does not differ from "D" or "E" nor does "D" from "E," since in each of these instances less than two and a half intervals separate the mean values depicted. Similarly the significance of the difference between any two values can be ascertained.

The value for "F" is shown in Tables 2 and 4 and at the top of each bar diagram. In all instances, with the single exception of the hemoglobin determinations on the men, "F" is preceded by a plus

sign, indicating that the variance between individuals was in every case but one greater than the variance within individuals. Moreover with reference to the human material, the value for "F" was significant ($P < 0.01$) as regards the following eleven cell factors: red



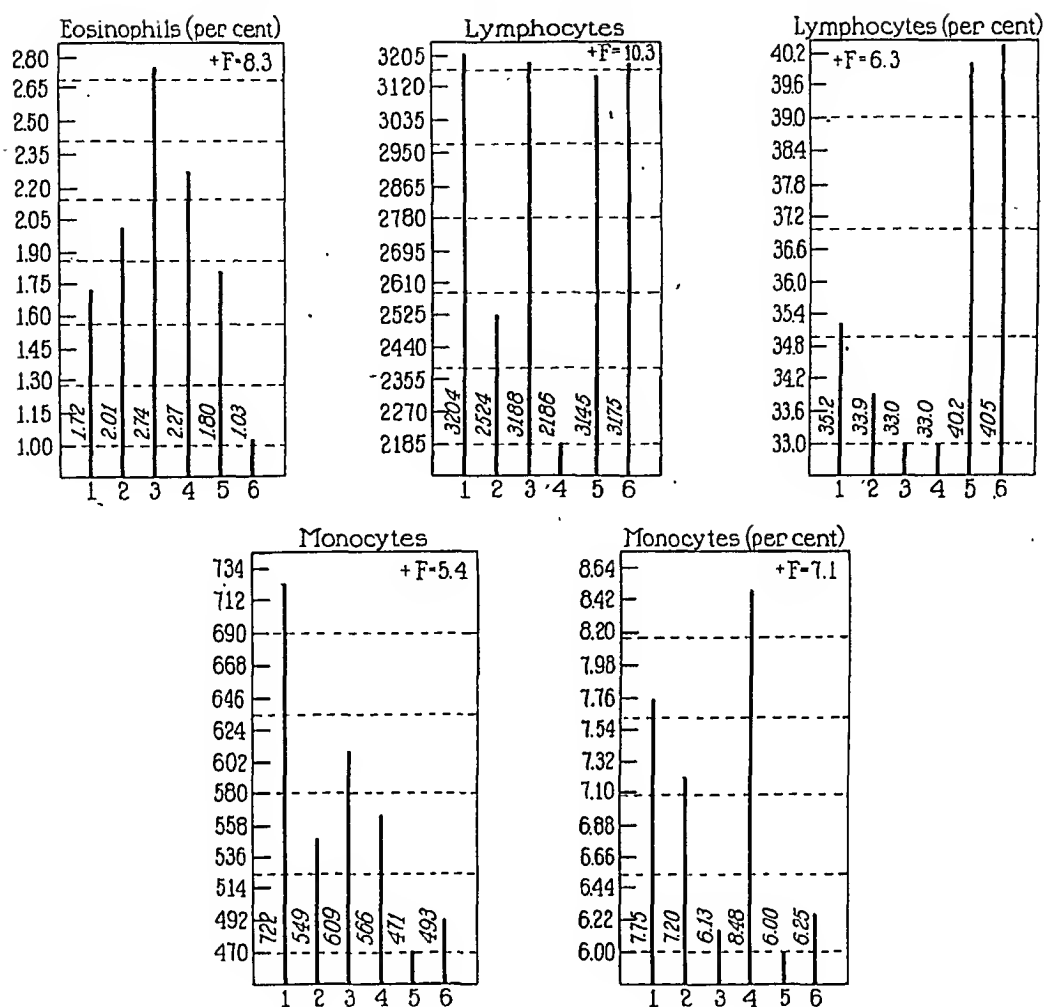


FIG. 2.—Quantitative variations in the blood cytology of healthy rabbits. See text for explanation of horizontal broken lines and significance of "F." 1, 2, 3, 4, 5 and 6 represent different individuals.

cell count; total white cell count; neutrophils, basophils, eosinophils and lymphocytes in absolute and relative numbers; and monocytes in absolute numbers. "F" was probably significant ($P = 0.01+$ to 0.05) with regard to the platelet count. This indicates that for the factors enumerated significant heterogeneity was found to exist among the individuals studied. Although for monocytes in per cent the variance between individuals was greater than the variance within individuals, tending to demonstrate heterogeneity, the value for "+F" in this instance was not significant. In the case of hemoglobin, the within classes variance was greater than the between classes variance. The difference was however not significant and homogeneity cannot be said to exist.

As far as the rabbit material is concerned, significant heterogeneity among individuals was demonstrated for every factor with the exception of the platelets. In this case the tendency was toward

heterogeneity, but the variance between the means of individuals was not significantly greater than the variance within individuals.

Discussion. The evidence which has been presented indicates that healthy individuals differ widely with respect to their composite blood formula. These differences are all the more striking since they have been shown to occur not only among healthy young men but also among healthy rabbits. In the biometric sense significance is largely a function of the number of observations on a variable, and it is therefore safe to presume that a similar analysis of larger numbers of individuals, with more observations on each than is contained in the present material, would demonstrate highly significant heterogeneity among individuals as regards all of the blood elements studied. This surmise is supported by the fact that with 51 counts on each of 6 rabbits, highly significant heterogeneity was demonstrated for 13 out of 14 blood elements, while the human material, comprising fewer individuals and fewer counts on each, gave evidence of highly significant heterogeneity for only 11 of the 14 factors.

It should be emphasized that the men and rabbits were all in a state of good health throughout the investigation. With 3 exceptions all of the mean values were within the usually accepted limits of normality. The exceptions referred to are the mean red cell count for the young man "A," and the eosinophil counts for the men "B" and "E." Although "A's" mean red cell count of 4.29 ± 0.06 millions appears to indicate an anemia, this individual has maintained a state of excellent health for 4 years following the reported studies, and moreover repeated counts during this subsequent period have indicated no deviation from this mean value. At no time has his red cell count ever reached five million.

The reason for the high eosinophil count of "B" and "E" is not known with certainty. A plausible explanation would ascribe it to the epidermophyton infection which both of these individuals periodically presented. In this connection however, 3 points should be emphasized: First, that the infections were never severe enough to cause discomfort; second, that high counts were noted during periods when evidence of the affection was absent; and third, that "A" with the lowest eosinophil count was also subject to this disorder. If the explanation for the high eosinophil counts of "B" and "E" is accepted, it is difficult to understand their reactivity to the epidermophyton, and the non-reactivity of "A" to the same stimulus. The suggestion is offered that inherent or constitutional differences among these individuals were largely responsible for their differing reactivity.

Other workers have called attention to what has been termed familial eosinophilia, and it is possible that individuals "B" and "E" fall into this category. Klinkert¹² described a family of 7, 6 of whom had eosinophil counts ranging from 6.2% to 15%. More recently Stewart¹³ studied 4 families in each of which several indi-

viduals presented distinct, persistent and unexplained eosinophilia. In none of those so affected could careful investigation reveal any of the known causes of eosinophilia, particularly dermatoses, allergic states or parasitic infections. The eosinophil counts in one of Stewart's families were as follows: father, 2%; mother, 6%; daughters, 10% and 10%; son, 42%. Another remarkable example of familial eosinophilia was the following: mother, 20%; father, 17%; daughters, 32% and 28%; father's brother, 15%; mother's sister, 15%; mother's brothers, 22% and 15%. There was no blood relationship between the father and mother of this family. Poindexter¹⁴ has called attention to the high eosinophil levels among the colored people living in and around Union Springs, Alabama. The average eosinophil count for 158 individuals between 15 and 30 years of age was 8.6%. In none of them was there a positive malarial smear, a positive tuberculin test, parasites in the stool, or any disease generally associated with eosinophilia.

The young men of the present study were all in good health, in the same decade of life, living in a nearly uniform physical environment, and ingesting approximately the same type of food. The rabbits were supervised more rigorously. Their age, food, and physical environment are known to have been as nearly uniform as laboratory control could make them. The blood counting technique had been standardized by several years of technical improvement, and the studies on the several individuals were carried out by the same observers at the same time of the day, and same day of the week. In spite of this uniformity of environment and of technique, statistically significant differences were demonstrated among the individuals comprising each of the two groups. In the light of our present knowledge, the explanation of these differences is largely a matter of conjecture. It is within the realm of possibility that subclinical infections, or cryptogenic organic disorders might have been responsible for the observed differences among individuals. A more tenable hypothesis however, is suggested by the well-recognized variability of biologic phenomena, particularly of such characteristics as body build, physical conformation, degree of pigment, etc. This hypothesis would ascribe the hemacytologic variations to inherent or constitutional differences among individuals. On this basis the potential blood cell level of an individual is determined by genetic factors, and is as characteristic of that individual as his physical type, the color of his eyes, and even his finger prints. This inherent potentiality is of course subject to the conditioning influence of environmental stresses such as disease, but fundamentally it characterizes and typifies the individual.

The practical implication of this study to the clinician is perhaps of more immediate importance. From the foregoing discussion it is evident that a blood cell count which is normal for one person may in fact be abnormal for another. A total white cell count of 9000 for individual "A" would be within the limits of normal for

him, since it is less than his mean white cell count plus two and one-half times the standard deviation ($7036 + 2\frac{1}{2} \times 896 = 9276$). On the other hand, the same total white cell count of 9000 would represent a pathologic leukocytosis for "E" since this value is greater than "E's" mean count plus two and one-half times the standard deviation ($5779 + 2\frac{1}{2} \times 921 = 8081$). In the same way a red cell count of 3.7 millions for "A" would be within that person's normal range, while the identical count for "B" would be outside his normal limits. If "B" had a neutrophil count of 2000 it would be of little or no clinical importance because this value is inside his normal range ($3075 - 2\frac{1}{2} \times 483 = 1868$) but the same count for "C" would represent a pathologic neutropenia ($4207 - 2\frac{1}{2} \times 623 = 2650$). This study therefore emphasizes the advisability of repeated counts on individuals during health in order to ascertain the numerical variability of each blood-cell constituent. With this knowledge of the blood cells' variability during health as a background, minor fluctuations which would ordinarily be dismissed as of no clinical importance would be assumed to indicate a departure from a healthy status, or in other words, a reaction to a pathologic process.

Summary.—1. Weekly or biweekly complete blood examinations were conducted on a group of 5 healthy young men and 6 healthy rabbits. The rabbits were examined over a period of 2 years, the men for 1 year. The mean values for each of the blood-cell elements of each individual were then calculated from these repeated observations, and a comparison of the individuals in each group with regard to these mean values was made.

2. Statistically significant differences among the men were demonstrated for the following blood factors: red cell count, total white cell count, and neutrophils, basophils, eosinophils and lymphocytes in absolute and relative numbers, and monocytes in absolute numbers. Statistically significant differences among the rabbits were observed for the following: red cell count, hemoglobin in per cent, total white cell count, and neutrophils, basophils, eosinophils, lymphocytes and monocytes in absolute and relative numbers.

3. The evidence indicated that healthy individuals differ widely with respect to their blood formula. These differences were all the more striking since they were shown to occur not only among healthy men, but also among healthy rabbits. It was suggested that the observed differences were due to inherent or constitutional variability among individuals, and that each individual has a characteristic and typical blood formula which is largely determined by genetic factors.

4. The evidence further indicated that a blood-cell formula which is normal for one individual may in fact be abnormal for another. It was therefore suggested that repeated blood-cell counts on individuals during health should be made in order to determine the

numerical variability of the different blood elements. With this information as a background, minor fluctuations which would ordinarily be dismissed as of little or no clinical importance, might be recognized as indicative of an early pathologic process.

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REACTION FOLLOWING INTRA-GROUP BLOOD TRANSFUSION.

IRREGULAR AGGLUTININ DEMONSTRATED BY THE SENSITIVE
CENTRIFUGE TEST METHOD.

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A NUMBER of cases have been reported in which transfusion of blood between members of the same group has been followed by a typical reaction syndrome of chill, fever, hemoglobinuria, suppression of urine, and azotemia, which may or may not terminate fatally.¹

While incompatibility of the bloods has been suspected, no etiologic factor has been consistently demonstrated. The prophylaxis remains obscure.

We have recently seen a reaction of this type.

Case Abstract. Mrs. C. was admitted to the maternity ward of the hospital and given a trial labor at the term of a normal pregnancy. Failing to make progress she was delivered by Cesarean section. Considerable blood was lost. Two days later she was given a blood transfusion from her husband who was found to be of the same group (O). Direct cross-matching of the bloods in hanging-drop preparations with 20 minutes incubation at 37° C. showed no evidence of agglutination under the microscope.

At the completion of the transfusion the patient had a chill and her temperature rose to 105° F. This was followed by hemoglobinuria and oliguria for several days, during which time the blood T.N.P.N. gradually rose to 235 mg. per 100 cc. The patient's condition was regarded as critical by the clinicians who saw her. She was given symptomatic treatment, the details of which are outside the scope of this paper. After a very anxious period she gradually recovered; at the end of 7 weeks she was symptom-free and had a normal T.N.P.N. and urine. The patient had never been transfused prior to this time. She gave no history of allergic manifestations.

The compatibility of the bloods was repeatedly checked by the hanging-drop method using the original materials; the original findings were confirmed. This method has been used here and in other hospitals in this city over a period of years without encountering a reaction of this type. The demand for speed in clinical work ordinarily precludes the use of highly sensitive methods. So far as we are able to judge the hanging-drop method is in general use in clinical laboratories.

The compatibility of the bloods was investigated by the centrifuge test method suggested to Wiener and Vaisberg² by Landsteiner and Levine. By this method we found that the original sample of recipient's serum agglutinated the cells of the donor. Twenty-four Group O donors were tested by this method; the cells of 23 of these were agglutinated. One (Case 22) was found to be compatible. Neither of the patient's parents were tested. The same individuals were tested by the hanging-drop method. The results of these tests are compared with the results of the centrifuge test method in the table on page 473.

The centrifuge test method was immediately included as a part of the routine procedure.

Samples of the recipient's serum were sent to Dr. Karl Landsteiner who tested it by mixing 1 drop of saline, 1 drop of serum, and 1 drop of 2 to 3% blood suspension in small tubes of 7 mm. diameter. Readings were taken after the mixture had stood at room temperature. Twenty out of 23 Group O bloods with which he tested it were agglutinated. He demonstrated that the agglutinin was not related to either of the factors M or N.

TABLE 1.—COMPARISON OF CENTRIFUGE AND HANGING-DROP METHOD.

Recipient's serum plus cells of donor:	Date: Method: Technician:	11-3-35		11-4-35.	
		Centr. meth. A. W. R.	Hanging-drop.		
			A. W. R.	E. S. H.	
1 . .		+++	0	0	
2 . .		+++	0	0	
3 . .		++	0	0	
4 . .		+++	+ -	0	
5 . .		+++	0	0	
6 . .		+++	0	0	
7 . .		+++	0	0	
8 . .		+++	0	0	
9 . .		+++	0	0	
10 . .		+++	+	0	
11 . .		+++	++	+	
12 . .		+++	0	0	
13 . .		+++	+	0	
14 . .		+++	tr.	0	
15 . .		+++	+	0	
16 . .		+++	++	0	
17 . .		+++	0	0	
18 . .		+++	0	0	
19 . .		+++	+.+	0	
20 . .		+++	tr	0	
21 . .		+++	0	0	
22 . .		0	0	0	
23 . .		+++	+++	+++ (Hemol.)	
24 . .		++	0	0	

In commenting upon the findings Dr. Landsteiner notes that the agglutination in this case is considerably stronger than in most other cases of irregular agglutination reported in the literature.

Our own experience affords no previous cases for comparison. One specimen of Group O blood tested with this serum by the centrifuge method exhibited agglutination as follows:

Serum.	Agglutination.
Undiluted	3 plus
1 to 5 dilution	2 plus
1 to 10 dilution	1 plus

Although its thermal amplitude was not carefully investigated this agglutinin was not noticeably more active at ice-box temperature. Both the laboratory and clinical evidence indicate that it retained some activity at 37° C. This again is contrary to the behavior of most irregular agglutinins that have been reported.

A short time later a similar agglutinin was demonstrated by the centrifuge test method in the serum of a prospective recipient; it had been passed unnoticed in the hanging-drop preparation. This serum agglutinated three Group O bloods tested. The fourth prospective donor (mother of the recipient) was found compatible by both methods. A transfusion of 550 cc. of blood was given with no indication of an unfavorable reaction. Although we attach no significance to the fact, it should be noted that in both cases the intragroup agglutinin was demonstrated during the puerperium.

In our laboratory at the present time the routine procedures in choosing a blood donor include:

- I. Grouping the patient (by using sera of Groups A, B, and O).
- II. Selection of a prospective donor of the *same* group.
- III. Cross-matching (recipient's serum with donor's cells, and donor's serum with recipient's cells) by both:
 - (a) Hanging-drop, and
 - (b) Centrifuge-test methods.
- IV. Kline test of the donor.

Technique for the Centrifuge Test Method: 1. Place 3 drops of serum in a small test tube (14 mm. diam.).

2. Add 1 drop of cell suspension (3 drops of blood from a 20-gauge needle in 4 cc. of a physiologic saline solution containing 0.2% sodium citrate).

3. Shake to mix. (A control of saline and cells is optional after a little experience.)

4. Incubate 5 minutes at 37° C.

5. Centrifuge 3 minutes at high speed.

6. Note any evidence of hemolysis.

7. Shake the tubes to resuspend the cells while observing them with a concave mirror or hand lens. Note any evidence of clumping.

8. Pour the fluid onto a glass slide and examine microscopically for agglutination.

In our experience this test has not given false positives. Rouleaux formation and pseudoagglutination are less troublesome than in slide methods. In case of question they may be ruled out by repeating the test, using a 1 to 5 dilution of serum. Centrifugalization permits the observation of hemolysis, which rarely may mask agglutination. At the same time agglutination is so sensitized that the research standard of sensitivity is attained without loss of the clinical virtue of speed. While this routine may sound cumbersome, we find that the centrifuge test can easily be set up and completed during the incubation period of the hanging-drop preparations. This additional routine has not slowed up the laboratory service. While it is probable that the hanging-drop method eventually may be discarded, we are not yet ready to do this.

Summary and Conclusions. The relation of anomalous agglutinins to transfusion has been an unsettled question.³⁻⁶ It might be questioned that the agglutinin was responsible for the reaction in this case. However, the facts may be summarized as follows: a Group O patient was given 500 cc. of Group O blood; the cells of this blood were susceptible to agglutination by an anomalous agglutinin of low titer existing in the serum of the recipient. The recipient exhibited the typical symptoms of a delayed transfusion reaction, followed a typical course, and eventually recovered. A second patient, exhibiting a similar anomalous agglutinin, was given 550 cc. of blood compatible with her intragroup agglutinin and no sign of reaction was observed. Until the contrary is shown we shall continue to regard incompatibility resulting from anomalous agglutinins as a definite contraindication to transfusion with such a blood.

In each of the 2 cases the low-titer intragroup agglutinin was unobserved in the routine compatibility tests by the hanging-drop method although it was readily demonstrated by the centrifuge test method.

It is suggested that the use of the centrifuge test method in clinical practice may aid in avoiding transfusion reactions of the type mentioned above.

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SPLENECTOMY IN THE TREATMENT OF SUBACUTE BACTERIAL ENDOCARDITIS.*

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IN subacute bacterial endocarditis as in Hodgkin's disease we know we are beaten from the start. Remissions may occur, raising the elusive hope of recovery but the end is early death. There are a few exceptions to this in subacute bacterial endocarditis but they are so few as to be negligible. We feel somehow that the patient infected with the mildly pathogenic *Streptococcus viridans* ought not to die. If the streptococcus is only a secondary invader as several authors maintain, then it behooves us to find the primary factors that enable it to become so irresistible an enemy. The interesting point made by recent writers that subacute bacterial endocarditis is only another manifestation of rheumatic infection needs further investigation. Our own impression is to the contrary.

Every imaginable agent and procedure has been used and practically all have been failures. This tragic fact led one of us a few years ago to the following reflections. Is it possible that death is due chiefly to the manufacture of bacteria and toxins in secondary

* Read at the Meeting of The Association of American Physicians, Atlantic City, May 5, 1936.

foci and if so, is the spleen not likely to be the most important branch factory? In the majority of cases the spleen is greatly enlarged and the seat of multiple infarctions. Furthermore, in what is perhaps an analogous situation, syphilitic splenomegaly, it has been found that treatment is sometimes unavailing until after splenectomy.

On the basis of these considerations one of us,¹ in 1918, proposed splenectomy as a therapeutic procedure in subacute bacterial endocarditis and reported a case which is briefly summarized here, as Case 1.

Case Abstracts. CASE 1.—The first case was that of a man, aged 57, father of a medical colleague. On account of a large spleen and anemia with leukopenia the diagnosis of splenic anemia had been made. However, the finding of petechiae, the presence of a valvular murmur and the long-continued fever justified the diagnosis of subacute bacterial endocarditis, although the spleen was larger than is usually seen in such cases. As nothing had helped the patient, he and the doctors concerned readily accepted the suggestion of splenectomy. The organ was found to be the seat of numerous infarctions. So striking was the improvement that it encouraged the hope of cure. However, 4 weeks later the patient developed an abscess of the larynx from which he died.

CASE 2.—The second case is that of a married woman, aged 25, who had two attacks of rheumatic fever, one at 11, one at 14. At the age of 20 she had auricular fibrillation lasting 2 weeks. Her marriage was followed by two pregnancies that had to be terminated artificially because of the condition of her heart. On June 20, 1935, she consulted one of us because of a tired feeling and painful subcutaneous nodes on fingers and toes. Physical examination showed marked cardiac enlargement, a mitral systolic murmur and 2 painful ecchymotic nodes. Her general appearance was, however, that of a woman in good health. Blood culture yielded a Gram-positive nonhemolytic streptococcus. The patient complained bitterly for a few weeks of pain in the right hip joint and in the abdomen. The blood counts are given in Table 1. Throughout the patient's illness the urine aside from a trace of albumin was entirely normal.

In addition to general supportive measures several specific forms of treatment were instituted—blood transfusions and specific bacteriophage therapy—the phage was kindly prepared by Dr. J. W. P. Love. It proved unavailing and this was also true of snake venom therapy. A total of 10 cc. of a 1 to 3000 solution of moccasin snake venom was administered. There was a transient lessening of the severe hip-joint pain, but after a few injections the pain returned and was worse than ever. The slightest jarring of the bed would make the patient cry out with pain.

It was decided to remove the spleen which had been palpable since early in July, 1935. At the operation the organ was found large and infarcted. Two pea-sized accessory spleens were also removed. There was immediate relief of joint and abdominal pains, an improvement in the red cell count and hemoglobin percentage, no further loss of weight, the heart became quiet and as the patient often stated "it had ceased to tumble about so." The fever continued and seemed to exhilarate her. She saw her friends, played bridge in bed and did not seem to realize that she was critically ill. There was no let-up however in the showers of emboli in the fingers and toes. On December 16, the patient began to develop thick-ness of speech and nocturnal Cheyne-Stokes breathing which were interpreted as of cerebral embolic origin. On January 1, 1936, she was seized with convulsions and died on the following day.

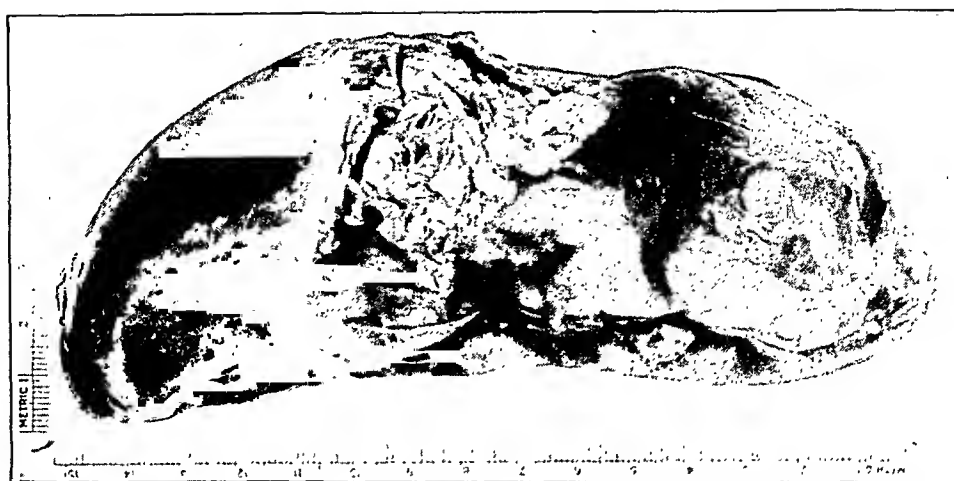


FIG. 1.—Case 2. Enlarged spleen showing wide vascular band of adhesion.

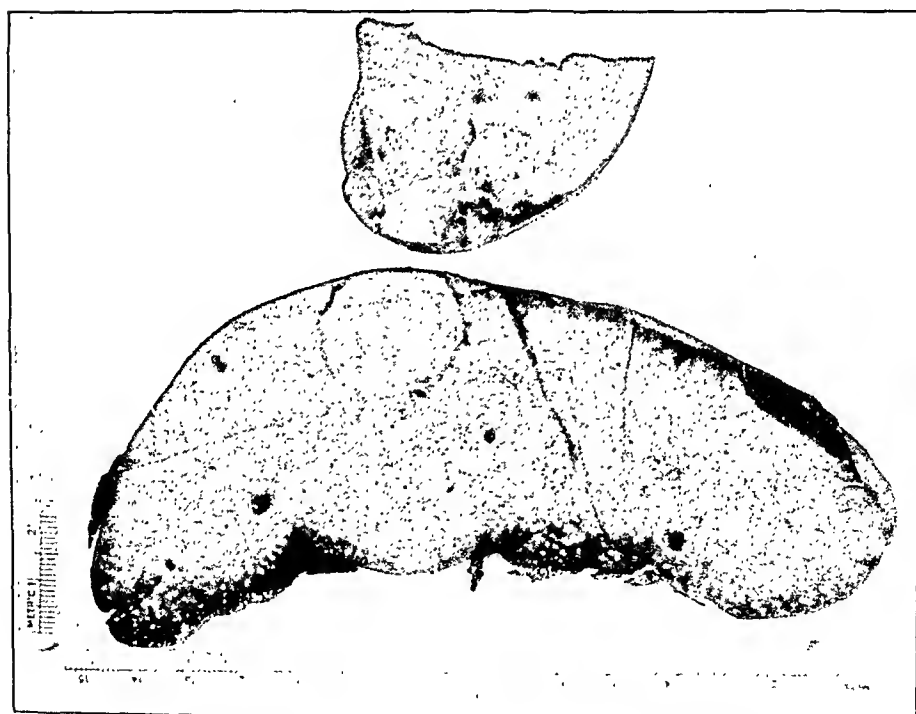


FIG. 2.—Case 3. Section of spleen showing infarcts.

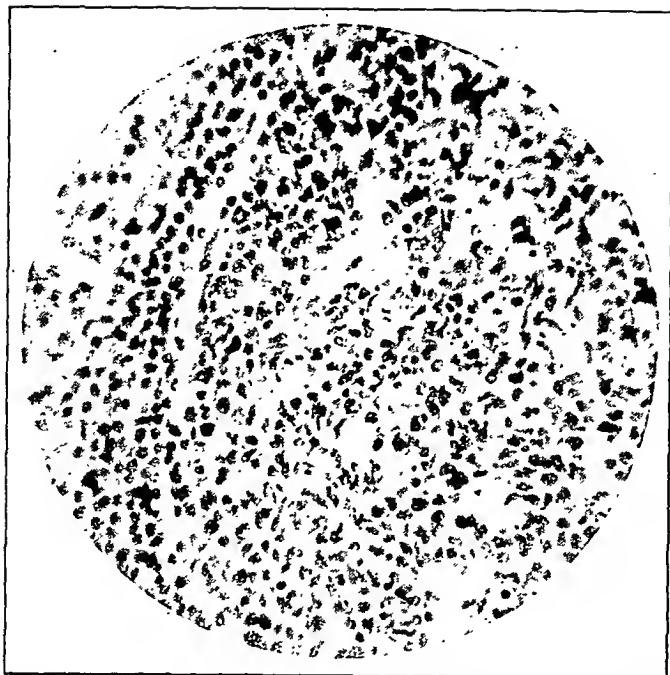


FIG. 3.—Case 2. Part of a lymph follicle near the periphery. Within the follicle are seen histiocytes and neutrophils. In the perifollicular area are found neutrophils and eosinophils among other cells. ($\times 243$.)

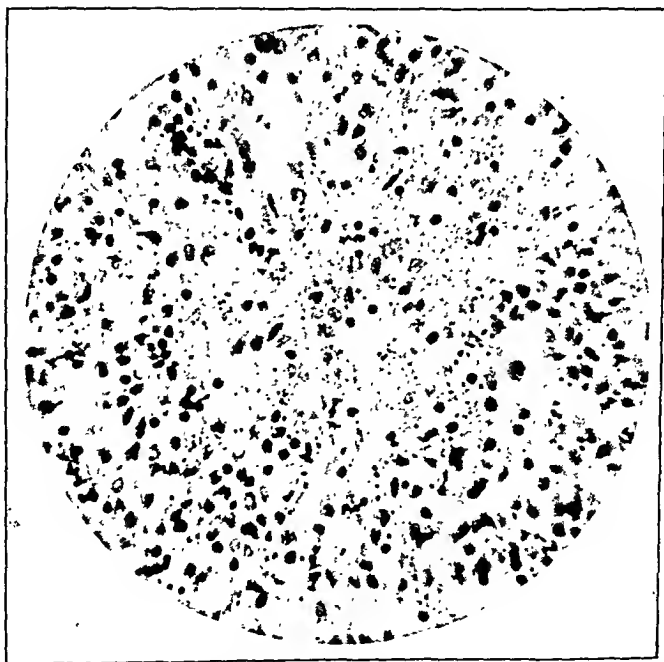


FIG. 4.—Case 2. The splenic pulp. The sinuses contain a large number of neutrophils, lymphocytes and histiocytes. In the pulp proper, there is an accumulation of plasma cells around the bloodvessels. A moderate amount of fibroblastic proliferation is present. The iron pigment is not very abundant. ($\times 243$.)

Examination of the Spleen. Gross Morbid Anatomy. The main spleen was at least twice normal size, of firm consistency, deep red in color and covered by a fine frost of fibrinous exudate. A strong, wide, vascular band of adhesion connected the visceral surface and anterior tip of the spleen to the cardiac portion of the greater curvature of the stomach (Fig. 1). After 10 days in formalin, the spleen weighed 13 ounces (404.3 gm.). A cross-section exhibited large lymphoid aggregations over the entire cut surface, except where the infarct presented itself.

Histologic Examination (Dr. Paul Klemperer). Follicles: These are really large, with centers particularly conspicuous. There is a great number of reticulum cells. But there are also neutrophils within the center of the follicles. Around the follicles, in the perifollicular zone, there is a great accumulation of leukocytes and eosinophils among other cells.

Red Pulp. The sinuses and sinus epithelium are not particularly conspicuous. The sinuses contain a large number of neutrophils, lymphocytes and histiocytes. In the pulp proper there is an accumulation of plasma cells around the bloodvessels. Moderate fibroblastic proliferation is present. There is a good number of pale nucleated cells (histiocytic cells) which contain iron pigment. The iron pigment is not very abundant (Figs. 2 and 3). Gram-stained sections: no bacteria found.

TABLE 1.—THE BLOOD PICTURE IN CASE 2.

- *Pre-operative.**

Date.	R.B.C., millions.	Hb., %.	W.B.C.	Neutro- phils, %.	Band forins, %.	Eosino- phils.	Baso- phils.	Other lymph.
6/22/35	3.9	74	9,900	63	8	0	1	36
7/ 9/35	3.8	79	10,300	75	†	0	2	23
7/24/35	†	76	10,800	75	†	2	1	22
7/30/35	†	83	7,400	70	12	0	2	28
8/ 3/35	4.4	84	6,800	75	15	1	0	24
8/ 7/35	†	†	8,000	61	8	1	1	37
9/14/35	3.7	65	12,800	78	†	2	0	20

Postoperative.

9/19/35	4.1	66	14,300	77	15	5	0	18
9/24/35	3.8	74	21,600	79	10	5	0	16
10/ 1/35	3.5	70	14,700	72	14	2	0	26
10/ 8/35	4.1	73	21,100	75	14	2	1	22
10/23/35	4.1	75	14,700	70	9	1	0	29
11/20/35	4.0	73	26,600	77	20	1	0	22
12/16/35	4.4†	67	29,900	73	12	0	1	26

* The platelet count before splenectomy was average normal (no actual count was made, but that is the note that appears on the blood count sheet as of July 24, 1935). Following splenectomy platelet counts were made on September 19 and 24 and October 1 and 8; these were found, respectively, to be 356,700, 253,440, 310,000 and 258,000.

† The blood count should be evaluated in the light of the presence of edema—the patient had gained 5 pounds of fluid in 2 weeks, although there was only slight pitting on pressure of the dorsum of the foot; a slight clubbing of the fingers, from which the blood for counting was taken, was also present, but this was present from the beginning. (Clubbing of fingers first noted, September 29, 1935.)

† Not done.

CASE 3.—I. A., a youth aged 22, was seen in consultation with Dr. Blumberg by two of us on separate occasions. The patient presented the typical picture of subacute bacterial endocarditis. His illness had begun on March 25, 1935, with malaise, muscular pains and late afternoon fever. The symptoms and the laboratory data were characteristic of the disease. Blood cultures—many were made—were positive for *Streptococcus viridans*.

Despite every form of treatment the disease progressed rapidly downward.* A cerebral embolus produced hemiplegia and stupor. His condition was such that it was felt the end was near. The parents consenting to the operation, it was performed on September 15, 1935, by Dr. W. W. Babcock. The spleen was found enlarged and showed infarction.

Notwithstanding the patient's critical condition the operation was well borne and was followed by striking amelioration. Weight and appetite markedly improved; there was less pain and greater comfort, less sweating, slight reduction of the leukocytosis and greatly improved morale. Unfortunately this favorable course persisted for only 10 days, then the former picture returned. Death took place on December 22, a little over 2 months after the operation.

Examination of the Spleen (Dr. H. J. Lemon). *Gross Description.* The spleen measures 17 by 10.5 by 4.5 cm. It is reddish-brown. The capsule is smooth and the organ is fairly soft. Scattered over the surface are several slightly raised areas which are yellowish-brown, the largest about 1.5 cm. in diameter and 2 cm. in depth, which appear to be abscesses. There is also a small accessory spleen, 1.2 cm. in diameter (Fig. 4).

Microscopic Description. Numerous sections of the spleen show many Malpighian corpuscles, much larger than are normally seen. The enlargement is predominantly of the so-called germinal centers. These are surrounded by a broad zone of lymphoid cells. There are patchy areas of congestion present. Here the sinuses are filled with red blood cells and lymphocytes. In other areas the sinuses are partly empty but appear enlarged. The splenic cords appear thickened and contain many lymphocytes and neutrophils. Large areas of necrosis are present in which there are numerous collections of neutrophils. Active fibrosis is beginning around the edges of the infarcted areas.

Diagnosis. Subacute splenitis with infarcts.

CASE 4.—H. M., aged 39, had no history of rheumatic infection. His illness began in January, 1935, with lack of "pep," weakness, irritability, and so on. In February he had an attack of grippe from which he never fully recovered. On biliary drainage (Dr. H. S. Davidson), the culture yielded a nonhemolytic streptococcus. In May, the man felt somewhat better and continued at work but began to have late afternoon fever. Blood cultures were negative. Somewhat later a thorough study of the patient's case was made in Youngstown, Ohio—Hodgkin's disease and leukemia were suspected.

When seen in Atlantic City he had the typical symptoms of sepsis—chills, fever and drenching sweats. The heart sounds were exceedingly feeble, indeed scarcely audible, but there was no murmur and no arrhythmia. The liver was enlarged and slightly tender. The spleen was easily palpable.

TABLE 2.—SOME BLOOD COUNTS FROM CASE 4.

	8/10/35.	9/26/35.	11/4/35.	4/29/36.	5/11/36.
R.B.C. . . .	4,600,000	3,790,000	4,550,000	4,500,000	4,401,000
W.B.C. . . .	5,750	1,850	9,350	17,400	13,600
Hemoglobin . .	11 gm. (66%)	9 gm. (54%)	11.5 gm. (69%)	12.5 gm. (73.7%)	12 gm. (70.8%)
Eosinophils . .	0	4	2	1	1
Mononuclears .	19	14	16	9	12
Neutrophils . .	67	44	70	73	78
Lymphocytes . .	13	38	10	16	8
Basophils . . .	1	0	2	1	1
Color index . .	0.71	0.71	0.76	0.81	0.8

* The following were the more specific measures employed in this case: Intravenous and intramuscular injections of *Streptococcus cardioarthritidis* serum (Small) and concentrated polyvalent antistreptococcus serum, intravenous injections of bacteriophage prepared by Dr. John Love and one of us, transfusions of blood for a total of 19; intravenous injections of sodium cacodylate, and so on.

As the disease progressed the patient lost more and more weight, a total of about 60 pounds. His color became sallow, he grew weak and very irritable and had an extreme hyperesthesia of the skin of the entire body. The spleen was much enlarged and a little fluid could be detected in the abdomen.

No definite diagnosis was arrived at—mural subacute bacterial endocarditis seemed reasonable. As nearly every conceivable treatment had been tried without any result, splenectomy was suggested as a last resort. The patient readily acquiesced and the operation was performed by Dr. Babcock on October 1, 1935.

It was exceedingly well borne, and for about 8 or 9 days the patient appeared distinctly improved. However, on October 11 the temperature began to run in the same manner as it had prior to the operation, but on October 23 it suddenly dropped to subnormal. The patient had a convulsive seizure and was comatose, almost pulseless, and death was expected at any moment. Under stimulation he revived and from that time on his improvement was rapid and progressive. On November 4 he was discharged convalescent. He returned to work and when last seen was in very good condition.

Bacteriologic examination of the spleen revealed a pure culture of *Streptococcus viridans*.

It is difficult to explain the cause of the collapse of H. M. 23 days after the splenectomy, but following it there was no doubt of his rapid return to normal and a state of satisfactory health. During recent weeks he has had 3 periods of fever with pain in the left loin, sweats and leukocytosis. It is possible that he is developing a perinephric abscess, although the studies with that thought in mind have been negative. Whether the morbid process underlying these attacks is the same as that which afflicted him originally or whether what is going on now is something left over from the operation cannot at present be decided. Dr. Harold Davidson, the family doctor, is convinced that the patient was dying when we saw him together and that the splenectomy saved his life. He gained 60 pounds in weight and for 5 months has been to all intents and purposes a well man.

Examination of the Spleen (Dr. Frank Konzelmann). *Gross Description.* The specimen measures 18 by 12 by 6 cm. The surface is bluish-red and nodular. There is some wrinkling of the capsule. The pulp is moderately firm. The incised surface is a deep red; it is granular. The follicles are few and barely visible. The trabeculae are not marked. There are occasional translucent irregular whitish markings throughout the organ. There is no evidence of thrombosis of the splenic vein.

Microscopic Description. (Bouin fixation, hematoxylin and eosin.) The follicles are few in number; the number of lymphocytes composing them is also small with a decidedly eccentric arrangement of cells that are somewhat larger than ordinary lymphocytes and cells that have a somewhat more reticular nucleus. The periphery of these small follicles is frequently the seat of hemorrhage. In the interfollicular areas the usual splenic sinuses are almost obliterated by what seems to be swelling of the reticulum. The number of free cells and of lymphocytes seems to be distinctly diminished, while the number of reticulum cells, notably cells that have oval or elongated nuclei, seems to be increased. Occasionally a large cell measuring 30 to 40 microns in diameter with an equally large nucleus is seen. The nucleus of this cell consists of a deep-staining membrane, huge nucleoli and a very scant scattering of chromatin particles. Occasionally there are patches in which several giant cells occur, possessing 2, 3 or 4 nuclei of the type just described. These cells make one think of the Reed-Sternberg cell of Hodgkin's disease. However, the absence of the other cellular elements of Hodgkin's disease makes such a diagnosis improbable. Occasionally mitotic figures are seen among the reticulum cells. The striking feature is the relatively small amount of blood in the organ. There are

patches, especially around the follicles, as mentioned above, where vessels are engorged. An occasional engorged venule is seen, and very careful search reveals here and there pools of blood in very much distended sinuses. It seems as if these bloody collections are most numerous where nodules appear on the surface of the organ. It is also noteworthy that many of the arterioles are characterized by a hyalin degenerative process of the endothelial lining and sometimes of the tunica media. Examination with oil immersion reveals in some of the macrophages small granules that are suggestive of coccoid bodies. Nothing resembling Leishman-Donovan bodies can be discovered.

Diagnosis. Chronic splenitis showing hyperplasia of the fibrous and cellular reticulum.*

The literature on splenectomy in septic conditions, particularly in subacute bacterial endocarditis, is exceedingly meager. The senior author's case was apparently the first to be reported. Of 2 patients with subacute bacterial endocarditis operated in the Mayo Clinic, 1 lived 3 months, 1, 7 months after the operation. We found one article in the Russian literature by Sawadski² in which a successful splenectomy is reported. The case was not altogether typical of endocarditis but it was one of long-continued fever in a woman of 28 with a rheumatic history. Sawadski believes that the spleen may act as a focus of infection and says, specifically, that the presence of bacteria in the blood stream is no contraindication to the operation of splenectomy.

Persistent search has revealed a few additional articles. Wieden³ reports a series of cases of splenectomy from Prague. Among 81 instances of splenectomy, there were 5 cases of endocarditis in which the operation was done for infarcts of the spleen. The first case was that of a military officer of 21 who had had a long-standing sepsis following a grenade injury. After removal of the spleen, which was enlarged and contained several infarcts, the patient recovered completely. While the clinical diagnosis was endocarditis, the possibility of chronic sepsis secondary to wound infection cannot be excluded. The second patient, a man of 40, with a history of rheumatic fever, cardiac enlargement and a systolic and diastolic murmur, was evidently a case of subacute bacterial endocarditis. He died without any improvement in his condition 2 months after the operation. The third case, that of a young woman of 24, with the symptoms of subacute bacterial endocarditis, died 3 months after the operation. The fourth patient was a woman of 57 with symptoms of sepsis, a systolic murmur at the mitral area and enlargement of the spleen. On removal the spleen was found enlarged, with numerous infarcts and hemorrhages. The patient

* Since writing the foregoing article the patient, H. M., was operated upon in the suspicion that he might have a perirenal abscess. No abscess was found. He died in his home in Atlantic City on June 10. No autopsy was obtained. Dr. Kolmer, one of the attending physicians, thinks that death was due to subacute bacterial endocarditis. Whatever the nature of the process may have been, the fact remains that when splenectomy was done the patient to all intents and purposes was near death. He lived nearly 7 months and for most of that time was in good health and able to look after his business.

recovered, but 7 months later there was a recurrence followed again by improvement. A year after the operation signs and symptoms of lymphatic leukemia appeared and the patient died in coma. The autopsy showed lymphatic leukemia and mitral and aortic endocarditis. The fifth patient was a man of 27 with a history of rheumatic fever. He had a murmur and a large spleen. The spleen on removal was found to be the seat of infarcts the size of walnuts. On culture nonhemolytic streptococcus and staphylococcus were obtained. Death occurred 20 days after operation from cerebral embolism.

Vogel,⁴ in a lengthy article on extirpation of the spleen in diseases of the blood, says that he wants particularly to recommend splenectomy in the early stages of endocarditis lenta when the general state of the body is adequate and the heart lesion has not progressed too far. He does not think that the continued reinfection of the blood stream is derived from the vegetations on the valves which in the beginning are certainly very slight, but believes it not impossible that a chronic focus of infection such as might be in the spleen overflows into the blood. It is also possible that the bone marrow is a source of sepsis.

Nordmann⁵ performed splenectomy in a case of endocarditis in the belief that the spleen might be responsible for the continuance of the infection, by being a reservoir for bacteria and toxic substances. His patient had mitral stenosis and insufficiency as the result of an acute attack of rheumatic fever. Two years later the symptoms of subacute bacterial endocarditis manifested themselves. After 6 months of septic fever uninfluenced by treatment, Nordmann extirpated the infarcted spleen. The patient made a complete recovery and "long ago left the clinic a well man."

Münzer⁶ recommended splenectomy but reported no cases in which the operation had been performed.

We have found 1 case in the Spanish literature reported by Escudero and Merlo,⁷ of Buenos Aires. The patient at the age of 24 had had an attack of polyarthritis; later a syphilitic chancre for which he was actively treated. When 28 years old the signs and symptoms of subacute bacterial endocarditis appeared—there was mitral insufficiency, hypochromic anemia and severe pain in the left hypochondrium. Blood culture yielded *Streptococcus viridans*. Splenectomy was performed and was well borne. The hypochondriac pains promptly disappeared but the general symptoms were not changed. Four weeks after the operation the patient at his own request was permitted to go home and sometime later, the day is not given, he died of pulmonary embolism.

Heilborn⁸ reports 2 cases of splenectomy in endocarditis ulcerosa. The first was that of a man of 31. Two years previously he had an acute attack of articular rheumatism which left him with mitral insufficiency and stenosis. The symptoms of subacute bacterial endocarditis appeared 1½ years later. The spleen was enlarged and

tender. Blood culture was negative. After splenectomy the patient made a very good recovery and returned to work. The valvular murmurs were however unchanged. Six months later the man died from cerebral embolism, having previously had an infarct in the kidney. The second case was that of a man of 27 who had had articular rheumatism, gonorrhea, cholera and lues, for which he was actively treated. From January, 1921, onward he had a continual evening fever. The spleen which was much enlarged, was removed in March; 3 weeks later the patient suddenly became worse; signs of aneurysm appeared. A massive hemorrhage killed him on August 30. Heilborn concludes that cases of endocarditis ulcerosa, endocarditis lenta and chronic sepsis are favorably influenced by splenectomy if the clinical phenomena point to a pronounced participation of the spleen. It is important, however, to do the operation early. The removal of the spleen may prevent a continuing reinfection of the heart; perhaps it acts also by stimulating the reticulo-endothelial system. In any event the experiences to date justify further resort to operation.

There are unquestionably theoretical objections to the removal of the spleen in infective states. The spleen plays an important rôle in resistance and immunity through its large content of cells of the reticulo-endothelial system which are accepted as actively concerned in phagocytosis and in antibody production. Therefore, removal of the spleen would appear to be contraindicated from the point of view of removing an organ actively concerned in resistance and immunity. Furthermore, as Krumbhaar⁹ has shown, the removal of the spleen in normal animals causes a mild anemia, which however is temporary. The antianemic function of the spleen, depending perhaps upon its power to conserve iron, is readily taken over by the bone marrow and other members of the reticulo-endothelial system. The absence of stainable bacteria in the spleen of one of our cases suggests the further thought that the organ may actually destroy bacteria.

On the other hand, just as the resistance of the lymph nodes may sometimes be overcome so that they become the sites of abscess or tuberculosis, so the spleen is very commonly found to be the seat of infection during natural and experimentally produced infections. This is probably because the histologic structure of its pulp favors filtration and localization of organisms and especially of those occurring in the blood and peritoneal cavity. Furthermore, its histologic structure facilitates bacterial embolism and infarction, especially in the course of subacute bacterial endocarditis. Under the circumstances removal of the spleen may be beneficial in the way of removing a mass of secondary infection and thereby enabling the individual better to combat the primary infection.

Summary. 1. Splenectomy for subacute bacterial endocarditis is well borne even in far-advanced cases.

2. It has not so far been followed by a permanent sterilization of the blood stream in cases in which blood stream infection has existed.

3. Nevertheless, in every one of our cases life was unquestionably prolonged and made more comfortable. The physical and psychic improvement is most impressive. Even if the infectious process should continue in the heart, and it is possible that even this might be favorably affected, it seems that the general condition of the patient is improved.

4. Perhaps if the operation were done earlier in patients with palpable spleens and hearts not too badly damaged, the results might be better.

5. As death seems to be due in the majority of cases to embolism, the prevention of this complication should be taken into consideration. Nothing, we admit, may come of the attempt.

6. Treatment should not rest with splenectomy. Repeated small transfusions should be continued and bacteriophage therapy tried.

7. Splenectomy may prove to be a method of dealing with intractable forms of sepsis without discoverable focus in which splenomegaly is a prominent feature. This group, in which subacute bacterial endocarditis may be suspected but is unproved, at present promises the best results from the operation.

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GOUT—A FORGOTTEN DISEASE.

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FASHIONS in therapy may have some justification; fashions in diagnosis have none. Strangely enough, acute gout, one of the oldest maladies known to medicine, seems almost to have become

one of the forgotten diseases. Here is a definite clinical entity of which there is ample description and record and which in its ordinary manifestations is easy of recognition; and yet it seems to have become the fashion persistently to ignore it in the differential diagnosis of the arthritides. Is this not another example of the closing of the mind to the obvious—a fault that so seriously besets all medical diagnosis?

It may be well to recall certain historical facts about gout. First described by Hippocrates as podagra, cheiragra or gonagra, depending upon whether the toe, wrist or knee joint was involved, it was thought by him to be dependent upon the retention of humors. Galen suggested the unnatural accumulation of matters in the involved joints. Celsus advised the avoidance of corpulence in the prevention and cure. As early as the sixth century, Alexander of Tralles, a Greek physician, recommended a regimen with little meat, strict temperance, bleeding, and purging with colchicin. Rodulfe, in the thirteenth century, gave the disorder the name "gout" from the French "goutte," a drop; signifying that the "poison entered the joint drop by drop. Sydenham's seventeenth century treatise on gout remains the best clinical description of the disease. Wollaston, in 1797, was the first to approach the fundamental cause of this malady when he discovered that the "chalk stones" in gouty joints consisted principally of uric acid. Garrod, in 1847, demonstrated that abnormal amounts of uric acid could be recovered from the blood of patients suffering from gout, an observation which marked one of the first chemical approaches to the study of disease. Since then a further novel contribution is Llewellyn's suggestion that, in addition to a disorder of uric acid metabolism, there is an allergic factor. This writer cites examples of patients whose gouty attacks were provoked by hives, upper respiratory infections, asthma, typhoid inoculations and even gnats bite. He also points out that eosinophilia not infrequently accompanies these attacks.

One may well ask why a disease so long recognized, so well known and in general so easy of diagnosis is frequently overlooked. Perhaps one reason is the newly awakened interest in arthritis. In the recognition and treatment of the various forms of osteoarthritis, rheumatoid arthritis and specific infectious arthritis, the possibility of a chemical arthritis seems to have been largely ignored. In his enthusiasm for the new and important facts disclosed by the recent studies in this group of disorders the practitioner seems strangely to have forgotten gouty arthritis.

And yet, from the patient's standpoint, gout is the one type of arthritis in which we have most to offer. When recognized in the early acute stages the disease can be treated successfully in prac-

tically all cases, a statement which cannot be made safely about other arthritides.

Because of the effectiveness of therapy of this disease and of the serious consequences of its neglect it may be of value to set down our own recent experiences in acute gout, at the same time pointing out specific diagnostic pitfalls and calling attention to such general errors as may lurk in diagnostic fashions.

In an office practice, limited to internal medicine, we have been impressed with the frequency of recurrent gout and with the number of cases lacking a correct diagnosis for long periods of time. During the past 12 months we have observed 6 cases of acute gout in this office. This figure, while not large, indicates that this disease is not as rare as it is ordinarily supposed to be; since arthritis of any description is a complaint of but a small minority of our patients. In comparison, at the large arthritis clinic of the Presbyterian Hospital, during the past year but 5 cases of gout have been seen. This would indicate that the disease is much more common in private than in clinic practice, probably because of the higher standard of living among private patients.

Short summaries of the 6 cases recently observed is given:

Case Abstracts. CASE 1.—Mrs. J. P., a woman aged 55, with a tendency to obesity, never had any joint trouble until September, 1934. At that time, following mild trauma to the left great toe, it became greatly swollen, tender and red. The patient was seen by several physicians, had roentgenograms made with negative findings and was finally told her condition was an arthritis. By this time the process had spread to the other great toe and to the knee and hip. Treatment having brought no benefit, she finally insisted to her physician that she had gout, stating that her mother had had similar attacks of this disease. The uric acid of the blood was found to be 7 mg. per 100 cc. No colchicin or other specific treatment was given but the patient gradually improved. She first visited us during a minor attack of podagra in January, 1935. The uric acid of the blood was then 5 mg. per 100 cc. The attack yielded to colchicin in 24 hours. Upon a regimen the patient remained symptom-free, with the blood uric acid between 3 and 4 mg. per 100 cc. In January, 1936, the patient again reported with severe pain in the lower lumbar region. In this instance it was discovered that liver extract had been prescribed for a skin condition and that 12 capsules of this substance had been taken daily. The uric acid was 5.7 mg. The pains completely disappeared 48 hours after beginning the use of colchicin, and the patient has since remained well. Further uric acid readings have not been made.

CASE 2.—Mr. W. A. M., aged 55, complained of attacks of acute arthritis in ankles, knees and great toes, at intervals, for 12 years. They were usually acute and lasted 1 or 2 weeks. With each, a newly infected tooth had been found and removed, always with eventual subsidence of symptoms. The patient took no alcoholic drinks but was overweight and plethoric. He was first seen by us in October, 1935, during an attack of what had heretofore been called arthritis. There was swelling and tenderness of the left ankle and knee, also a phlebitis of the left leg. The uric acid of the blood was 7.2 mg. per 100 cc. Following treatment by colchicin

and diet the pain subsided promptly and the uric acid gradually fell to 4.4 mg. There has been no return of symptoms.

CASE 3.—Mrs. F. R., aged 69, complained of a severe monarticular arthritis of the left knee of 4 weeks' duration. She took alcohol in moderation and had been taking liver extract by mouth. The diagnosis had been arthritis despite negative Roentgen rays of the joints. Treatment by rest and heat was without relief. Pain prevented sleep. There was no extension to other joints. We first saw the patient in April, 1935. The left knee joint was tender, swollen and red over the inner aspect, with no excess of fluid. The uric acid of the blood was 4.6 mg. per 100 cc. A diagnosis of gout was made and colchicin given. The pain disappeared in 24 hours and there has been no recurrence. In January, 1936, the uric acid was 2.5 mg.

CASE 4.—Mr. E. R., aged 56, complained of intermittent attacks of arthritis for 4 years, with free periods between. His father suffered from a similar arthritis. The joints involved had been the knees and tarsus. Some of these episodes had kept the patient in bed a month. The diagnosis had been arthritis, the treatment symptomatic, but with little apparent influence upon the usual course of the attacks. The patient was first seen by us in November, 1935, in an attack involving both knees and the left great toe. A tophus was found on the right ear. The patient was overweight and took alcohol sparingly. The uric acid of the blood was 8 mg. per 100 cc. Roentgenograms were negative. After treatment by colchicin and diet the uric acid fell to 5 mg. and the patient has thus far enjoyed the longest period free from the disease since its first appearance.

CASE 5.—Mr. J. J. C., aged 40, was first seen in 1935, complaining of pain in the right great toe, ankle and shoulder of 10 weeks' duration. There was no family history of gout and the patient did not use alcohol. Several similar attacks had occurred previously. The involved joints were found to be swollen, tender and red. The uric acid was 7.5 mg. per 100 cc. With treatment by colchicin and rest the joint symptoms subsided promptly and have not returned. The uric acid is at present 4 mg.

CASE 6.—Mr. C. M., aged 38, complained of an acute arthritis of the right ankle and metatarsal joints of 3 weeks' duration. His condition was diagnosed as arthritis, but treatment with salicylates and heat brought no relief. This patient drank heavily and noted that an overindulgence in beer aggravated the joint symptoms. On physical examination the patient was found to be overweight and with marked swelling and redness over the metatarsal and ankle joints. Roentgenograms of these joints were negative. The uric acid of the blood was 5.2 mg. per 100 cc. A diagnosis of gout was made and, following treatment with colchicin and a diet, the arthritis subsided promptly. The patient subsequently left town and further history is not obtainable.

Comment. In reviewing these cases several significant facts are apparent. All of the patients have had a similar history; namely, intermittent attacks of acute arthritis, usually in the lower extremities, lasting from 1 to 4 weeks, with intervening free intervals. In our opinion this type of history is the most important single factor in the diagnosis of gout and is found in no other type of arthritis.

A large percentage of gouty patients have a positive family history of the disease.

All of our patients have been of sthenic habitus, overweight and in the age group over 35. While gout may occur in younger people and in those of asthenic type, it is uncommon in such.

The prevalent opinion that the use of alcohol is a factor in causing the disease is not borne out by our experience. But 1 of our patients was a heavy drinker; 2 were total abstainers.

Of interest is the fact that the ingestion of liver extract in relatively large doses was a possible factor in provoking attacks in 2 cases.

In this small series the uric acid of the blood has been not less than 5 mg. per 100 cc. in all cases with acute manifestations excepting 1. This laboratory determination remains a valuable aid in diagnosis. One should remember, however, that an attack of gout may occur without a significantly elevated blood uric acid and, further, that in patients with a history of the disease, a significantly elevated blood uric acid frequently occurs without an attack of arthritis.

In all of the cases cited the radiographs were negative. This is the usual finding in the more acute types of the disease.

The usual site of the arthritis is in the lower extremities, most often the metatarsal joints; next in frequency the knee and great toe joints. It should be pointed out, however, that the upper extremities may be involved as well and sometimes alone. Tophi are infrequent. We would reiterate that these statements apply to acute and not to chronic gout. The latter presents a different picture, which needs not be described here.

Of diagnostic value in these acute cases is the dramatic alleviating or curative effect of colchicin.

Our method of treatment is the administration of this alkaloid in doses of 1 mg. 4 times on the first day of the attack, then 3 times daily thereafter until symptoms subside or diarrhea occurs. After the attack, neocinchophen (tolysin) in 0.5 gm. doses and aspirin in 0.3 gm. doses are given 3 times a day for about a week. In addition, a diet low in purins is prescribed.

Summary. 1. The frequency of acute gout especially in private practice is emphasized, as is the too common failure to recognize it.

2. The recent increased interest in the infectious and degenerative arthritides has not extended to those of chemical origin, a trend which may have promoted some diagnostic failures.

3. All cases of recurrent acute joint inflammation with intervening free intervals, especially in patients of middle age, demand careful search for a family history of gout, a study of the uric acid content of the blood and, when indicated, a therapeutic test with colchicin.

4. Tophi and positive roentgenologic signs of gout are usually absent in acute cases.

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GOUT.*

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GOUT is now generally considered unimportant as a disease, and therefore the subject has been conspicuously absent in the recent literature. Gudzent and Holzmänn¹ found only 76 cases of true gout in 32,089 autopsies, while McCrae² quotes Fitcher as having discovered 59 out of 18,000 autopsies. I want to state that I have seen over 40 cases of gout during the past 5 years, and I now have 37 of these cases under my care. This suggests that the disease is more prevalent than has been supposed, and that previous criteria for diagnosis must be inadequate. When one examines the histories of these patients one soon discovers that most of them have suffered repeated attacks of gout, diagnosed "arthritis," for many years.

During the 25-year period from 1905 to 1929, it is estimated that there were approximately 414,296† admissions to the wards at Philadelphia General Hospital. In examining the records over this period, it was found that the diagnosis of gout was made only 47 times. The following is a table of the information which I have gathered from this group. Cognizance must be taken of the fact that complete studies in most instances were not available.

On the other hand, the following is a table of the cases studied from 1929 to 1935. During this period there were 146,992 patients admitted to the Philadelphia General Hospital. Among these it has been possible to make a positive diagnosis of gout 30 times. I am adding to these statistics 2 cases from the Jefferson Arthritis Clinic and 5 from my private records. It is interesting to note that 18 of my cases were from the Philadelphia Police and Fire Department.

* Read before the Medical Section of the College of Physicians of Philadelphia, May 25, 1936.

† The arbitrary number of 15,000 admissions yearly was taken from 1905 to 1911, inclusive, since the average for the subsequent 18 years was 17,000. Records for the exact number are not available.

TABLE 1.—FORTY-SEVEN CASES OF GOUT RECORDED AT THE PHILADELPHIA GENERAL HOSPITAL (1905-1929).

Age at onset:		41 to 50	10
21 to 30	7	51 to 60	1
31 to 40	8	Ages not stated	21
Duration of disease:			
1 to 5 years	10	15 to 20 years	5
5 to 10 years	5	20 to 30 years	4
10 to 15 years	3	Not stated	20
Males	44	Females	3
Colored	1 male	White	46
Positive family history	4	Not stated	22
Negative family history	21		
Lead	3	Alcoholics	10
Blood uric acid:		Elevated	8
Normal	3	Not studied	36
First blood uric acid reported by Dr. J. H. Austin, March, 1912; 7 mg. per 100 cc. blood. Normal value, 3 to 4 mg.			
Joints involved:			
Great toe	24	Joints other than great toe	12
Confined to great toe	12	Polyarticular	28

TABLE 2.—THIRTY-SEVEN CASES OF GOUT (1929-1935).

Age at onset:		41 to 50 years	7
10 to 20 years	4	51 to 60 years	5
21 to 30 years	5	Over 60 years	1
31 to 40 years	15		
Duration of disease before recognition:		11 to 15 years	9
At onset	7	16 to 20 years	6
1 to 5 years	4	21 to 30 years	4
6 to 10 years	5	Over 30 years	2
Family history:			
Negative in all police and firemen			
Other cases: Negative			15
Positive			4
Onset:			
Sudden			26
Gradual			11
Attacks precipitated by:			
Appendicitis			2
Acute infection			5
Trauma			4
Tonsillectomy			1
Length of attack, three days to 10 weeks			
Blood uric acid (mg. per 100 cc. of blood):			
Average high			6.96
Average low			5.06
Highest observed			19.00
Lowest observed			3.40
3 to 4.5 mg.		6 cases	
Above 4.5 mg.		31 cases	
Length of time treated:			
3 years or over			6
2 to 3 years			8
1 to 2 years			10
3 months to 1 year			13
Monarticular			8
Polyarticular			29

From these facts the natural conclusion must be drawn, that gout is not infrequent, but that the criteria for diagnosis have been inadequate. In the 37 cases herewith reported, the following features were of diagnostic significance:

1. It occurs at any age, but mostly from 20 to 50, and often with a positive family history.
2. It is usually polyarticular.
3. It may begin as an acute or chronic disease.
4. There are attacks and remissions, the patient being pain-free during the remission, even with deformity.
5. There may be but one attack yearly or there may be many.
6. The blood uric acid is usually but not always elevated. When not elevated, the diagnosis must be made on the history of repeated characteristic exacerbations and remissions.

The following 5 case studies illustrate various features outlined above.

CASE 1.—W. W., patrolman, aged 46, height 5 feet 11 inches, weight 195 pounds, was admitted to the Philadelphia General Hospital, February 27, 1932, complaining of pain in the left knee. This attack came on suddenly, 3 days before his hospital admission. There were no prodromal symptoms except that he felt weak and exhausted for 24 hours prior to the onset. The joints were red and swollen and the patient was unable to walk.

His past history was essentially negative except that he had his first attack 13 years before, at which time both knees were involved. The attack lasted but a few days. There was no edema or redness. Since then attacks usually occurred in spring and fall of each year lasting about 6 or 7 weeks, involving several joints at a time, namely, knees, elbows, and wrists. The patient developed tophi in the cartilage of his ears, and in his elbows and right wrist about 8 years previously. He knows of nothing that might have precipitated an attack. He had received baking, "medicine," and liniment for his pain. The diagnosis of arthritis and inflammatory rheumatism was made on different occasions until his present admission, at which time the diagnosis of gout was made and confirmed.

At the hospital large tophi from both olecranon bursa, right wrist and ears were removed. Tophi are still present in the left index finger and right metacarpophalangeal joint. He had been free from pain from January 15, 1933 to February 12, 1935.

Treatment consisted of purin-free diet and colchicin, $\frac{1}{100}$ grain, 3 times a day until the patient was well over the acute attack. He was then given the same drug, $\frac{1}{120}$ grain, 3 times daily for 1 week and a rest period for 3 weeks. Blood uric acid tests (mg. per 100 cc.) were as follows:

January 17, 1933	7.9 mg.
March 14, 1933	7.9 mg.
May 9, 1933	7.2 mg.
June 20, 1933	7.5 mg.
September 24, 1933	9.0 mg.
February 2, 1934	7.2 mg.

This patient had another attack February 12, 1935, and on questioning, admitted indiscretion in diet. He had also been drinking 2 bottles of beer daily for the previous few weeks. The blood uric acid, taken at monthly intervals, never returned to normal levels even though he was relieved of symptoms. It is to be noted that the pain did not begin in the great toe. It was deemed advisable to remove the large tophi, because ulceration is

accompanied by great suffering associated with the draining sinuses, and sometimes this lasts for many months. I believe that surgery is definitely indicated in all such cases.

CASE 2.—L. B., patrolman, aged 36, height 5 feet 7½ inches, weight 149 pounds, had his first attack of pain and swelling in the right great toe, which was preceded by itching in March, 1920. This lasted 4 or 5 weeks and was followed by pain and swelling of the entire right foot. The patient was confined to bed for 10 days, after which the foot apparently returned to normal. He has had 5 more attacks; in 1926, 1929, 1931, 1932 and 1934. These attacks occurred usually during March and subsided suddenly, with no lasting ill effects. In 1931, the pain developed after extraction of a tooth. Each attack has been less severe. The parts affected were as follows:

1920, pain and swelling in the right foot.

1926, severe pain in the left foot, great toe, and ankle. He was hospitalized 6 or 7 weeks.

1929, pain in the left foot, heel and ankle, lasting 3 or 4 days; relieved by strapping.

1931, following a cold he developed pain in the left foot, lasting 3 or 4 weeks.

1932, pain in the left foot lasting 1 month.

1934, pain in the left foot, great toe and right knee, following a cold.

The diagnosis of gout was made May 8, 1934. The blood uric acid was 8.2 mg. During the past year he was admitted to the hospital for the removal of a gangrenous appendix, and 2 days later developed an acute attack of gout, which lasted about 10 days. There are no signs of gout recognizable at present. Treatment consisted of a purin-free diet and colchicin $\frac{1}{8}$ grain, 3 times a day.

Case 2 illustrates the influence of infection in precipitating an attack of gout. It is easy to understand how a diagnosis of infectious arthritis might have been made under the circumstances.

CASE 3.—M. W., patrolman, aged 44, height 5 feet 8 inches, weight 170 pounds, was admitted to the Philadelphia General Hospital on December 1, 1933, complaining of pain in the chest, back of neck and shoulders, of 2 weeks' duration. This pain began in the left anterior chest and radiated to the scapula and back of neck. The onset of the pains was preceded by an attack of grip. The diagnosis of gout was made January 1, 1934. Blood uric acid tests were as follows:

January 2, 1934	Uric acid	8.8 mg.
		Urea nitrogen	14 mg.
January 12, 1934	Uric acid	4.8 mg.
March 27, 1934	Uric acid	4.2 mg.

No tophi were present and no signs of disease remained. He is still affected by the changes in the weather. Treatment consisted of purin-free diet and colchicin, $\frac{1}{8}$ grain, 3 times a day after meals. To date the patient has been symptom-free.

Case 3 represents another instance where the great toe was not involved, but it does illustrate the point so frequently made by textbooks that the blood uric acid returns to normal coincident with improvement in the disease. This, however, is not always true.

CASE 4.—J. Z., patrolman, aged 52, height 5 feet 8 inches, weight 155 pounds, had his first attack of pain in both ankles January 17, 1921. The

pain was more severe in the right ankle which was red and swollen, and lasted about 5 days. A diagnosis of acute articular rheumatism was made. Until March, 1932, the patient had had about 18 attacks of pain occurring usually in the fall or early spring. He knows of nothing which may have brought on the attacks; however, he noticed that the pain was aggravated if he ate meat or drank wine or beer. He was treated by his family doctor until March 24, 1927, when he was brought to the Philadelphia General Hospital, where the diagnosis of gout was made. He has been symptom-free since the above attack. This man presents typical tophi in the cartilages of his ears as well as moderate hypertension and arteriosclerosis. Blood uric acid tests were as follows:

March 28, 1933	Uric acid	7.8 mg.
March 30, 1934	Uric acid	8.8 "
		Urea nitrogen	29 "
		Blood pressure	150/100.
April 24, 1934	Uric acid	6.8 mg.
		Urea nitrogen	42 "
		Blood pressure	165/100.

Treatment consisted of a purin-free diet and colchicin $\frac{1}{170}$ grain, 3 times a day every fourth week.

Case 4 is an instance of gout with signs of renal insufficiency. There existed hypertension, arteriosclerosis, and not only a retention of uric acid, but of urea as well. Though the patient remains fairly comfortable as long as he adheres to instructions, the uric acid remains elevated and he can precipitate an attack of gout almost at will. The great toes are now involved, but this occurred fairly late in the disease.

CASE 5.—J. R., patrolman, aged 58, height 5 feet 10½ inches, weight 212 pounds, was admitted to the Philadelphia General Hospital in May, 1933, complaining of pain in the left great toe. He had had pain in this toe for about a month, but it was not severe enough to cause him to be hospitalized until the present admission. The joint was incised and wet dressings were applied for a period of 2 weeks after which the inflammation gradually subsided. He had no acute attacks of pain after the first attack.

The diagnosis of infected bunion was made until gout was suspected and confirmed by blood uric acid tests, which were as follows:

		Uric Acid.
July 25, 1933	9.4 mg.
November 14, 1933	7.7 "
January 14, 1934	4.8 "
April 10, 1934	5.2 "

Case 5 illustrates a classical attack of gout beginning with pain in the great toe, yet it was undiagnosed for many days.

Treatment. In the statistical study of the 47 cases presented from 1905 to 1929, it was found that while most cases were given up to a dram of wine of colchicum, rarely was one put on a purin-free diet. The usual dietary régime was a regular house diet. Hot magnesium sulphate solution was occasionally applied to the affected part, and salicylates were almost universally the drug of choice.

In the 37 cases herewith presented, the method of treatment was

divided into the treatment of the acute attack and treatment following the acute attack.

During the acute attack of gout, rest in bed, hot applications of saturated magnesium sulphate solution applied to the affected part, colchicin, and a liquid purin-free diet are of chief benefit. In addition supportive symptomatic treatment is given as necessary.

During the period of convalescence, the patient is put on colchicin, grain $\frac{1}{120}$, 3 times a day after meals and the purin-free diet is continued. After convalescence a purin-poor diet is prescribed and colchicin is administered grain $\frac{1}{120}$, 3 times a day after meals, for 1 week out of every 4. Blood uric acid determinations are done at monthly intervals. In cases in which the uric acid is elevated, we frequently find that this elevation continues or increases. When an elevation is discovered it becomes necessary to revert to the purin-free diet and a more active course of colchicin is instituted.

Deformities such as flat feet and contractures should be corrected as practised by the orthopedist. Infections should be cared for as one does for any other disease.

While cinchophen is efficacious in the treatment, colchicin should be used. Only one of my cases showed an idiosyncrasy to colchicin.

Treatment as described above has been highly successful. In the group now being attended, there have been but three recurrences. The patients have been treated for from 6 months to over 5 years. In each case where the disease recurred, the patient admitted indiscretions in diet or infection or trauma were the responsible factors. It is my firm belief that gout is controllable. With coöperation, the patient who would ordinarily suffer 4 to 6 attacks yearly, should no longer be troubled with this disease.

Summary. 1. A statistical study of 47 cases of gout from the admissions of the Philadelphia General Hospital, covering the period from 1905 to 1929, is presented.

2. An additional study of 37 cases covering from 1929 to 1935 is reported.

3. Attention is called to the frequency with which gout is seen in the Police and Fire Department of Philadelphia.

4. The treatment is invariably satisfactory as contrasted with other forms of arthritis.

5. Gout as a disease condition is met with fairly frequently in any large group of arthritics.

6. A revised set of diagnostic criteria are herewith submitted.

7. It is hoped that this study may lead to further studies of the incidence and treatment of gout.

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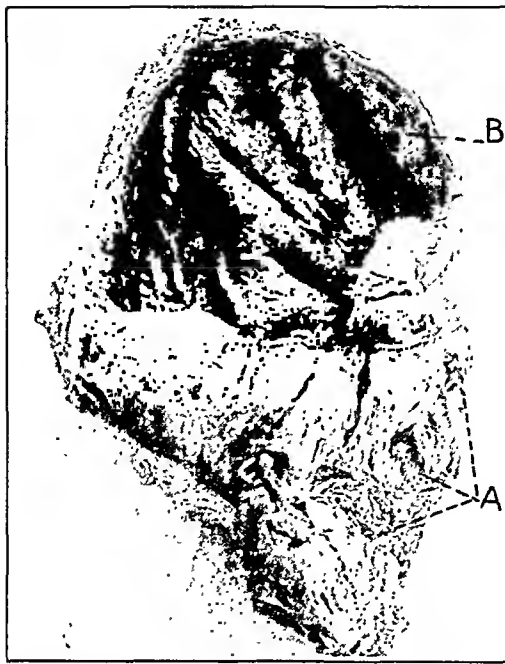


FIG. 1.—Prostate and bladder (one-third natural size) showing large abscess of prostate (*A*) and distended bladder (*B*) with hemorrhagic mucosa and markedly thickened wall.



FIG. 2.—A section of the prostate (low-power magnification) showing a large abscess cavity (*A*) filled mostly with neutrophils, a generalized round and neutrophil infiltration of the stroma with beginning fibroblastic proliferation and a few distorted acini (*B*).

seminal vesicles and vasa deferentia showed numerous honeycombed cavities, from which ill-smelling, muddy brown, purulent matter exuded. The fascia of Dénouvillier was tense but intact. The rectum, testes and urethra showed no abnormalities. Other findings of interest: lungs contained numerous minute subpleural abscesses; liver, a large subcapsular abscess in the right lobe; kidneys showed a number of small cortical abscesses, and beginning hydronephrosis. The spleen was enlarged to twice its normal size, and was soft and mushy. A pea-sized ulcer was found in the pre-pyloric region of the stomach.

On *microscopic examination*, prostate (Fig. 2) and seminal vesicles showed a widespread replacement by large abscesses made up of necrotic material with predominating neutrophil infiltration and beginning organization. A similar picture was seen in the liver, kidneys and lungs. *Cultures* from prostate, liver and lungs yielded pure growths of Friedländer's bacillus.

The final *pathologic diagnosis* was: purulent prostatitis and seminal vesiculitis with large abscess formation. Multiple pyemic abscesses in lungs and kidneys, and incipient hydronephrosis. Huge abscess of right lobe of liver. B. Friedländer septicemia. Healed tuberculosis of right lung. Acute splenic tumor. Ulcer of stomach. Coronary sclerosis and fibrosis of myocardium. Cloudy swelling of the viscera.

Discussion. Since the discovery of the organism by Friedländer in 1882, considerable change has taken place in our knowledge as to the rôle it plays in disease. At first, the organism described by him as "micrococcus" was believed to be the specific etiologic agent in lobar pneumonia. Later studies, however, have shown that the incidence of the Friedländer bacillus in lobar pneumonia averages no more than 5 to 10%,¹ the more frequent finding of this bacillus at autopsy being accounted for by pre-agonal or postmortem invasion. When found in the lungs *in vivo*, the Friedländer bacillus is either the result of a secondary infection, "contamination, or has reached the lungs from the gastro-intestinal tract, liver, bile passages or the genito-urinary tract."² The Friedländer bacillus, representing the large group of *Bacillus mucosus capsulatus*, is one of those Gram-negative bacilli which, from their habitat and pathogenicity, are related to the organisms of the upper respiratory tract; while from their biochemical and cultural behavior they are nearer to the bacteria of the gastro-intestinal tract of the coli-typhoid group. The bacillus is present in air dust, rotted potatoes, slivers, marshes and similar places, which makes contamination of the nasopharynx, gastro-intestinal and genito-urinary tracts a frequent occurrence. Etienne,³ in an exhaustive study comprising 83 cases collected from the literature, found instances of B. Friedländer infection occurring in almost every organ of the body. The name "pneumococcus" or "pneumobacillus" is therefore a misnomer. The lesions caused by this organism range from conjunctivitis, enteritis, cholecystitis, pyelitis, abscesses of the liver and kidneys, and involvement of the internal genitalia of both male and female, to subcutaneous pyemic abscesses, endocarditis and general septicemia.

Genito-urinary Infections. In the standard textbooks of urology there is little reference to B. Friedländer as a causative agent in

genito-urinary diseases. In the current literature, however, there are a number of such reports. Montt-Saavedro,⁴ Nicolaier,⁵ Chiari⁶ and Balog¹⁰ reported cases of cystitis, pyelitis, pyelonephritis and kidney abscess caused by the Friedländer bacillus. Bertrand-Fontaine and Parlier⁷ published a case of *B. Friedländer* pyelonephritis in a 5-year-old child following nasopharyngitis, with spontaneous recovery. Bernstein⁸ and Barcaroli⁹ reported cases of *B. Friedländer* epididymitis. Cain and Meyer¹¹ published a case of *B. Friedländer* infection supervening upon a latent nephrolithiasis. Brodny¹² observed a fatal case of *B. Friedländer* septicemia following transurethral prostatotomy.

In none of the old and recent articles did we find a case similar to ours. Cabot and Kretschmer¹³ state that they have not seen such a case. Balog¹⁰ cites a case of Sachs, of a *B. Friedländer* prostatic abscess without, however, indicating the source of the reference, and after a careful search no such report could be found in the literature.

It is possible that the paucity of reports of genito-urinary infections with this organism is due to the fact that pyemia and septicemia, with or without an additional mixed infection, which supervene in the majority of cases, mask the genito-urinary source of invasion. Other writers on the subject have also commented about the vagueness of the clinical picture and the lack of localizing signs in some of the obscure cases of prostatic abscess. The clinical picture in some of these patients simulated such diverse conditions as typhoid, paratyphoid, malaria, or the "grippe." Finally, there is the difficulty of positively identifying the Friedländer bacillus among its many strains and morphologic derivatives.¹⁴ It is therefore quite probable that other cases of prostatic abscess similar to ours have been hidden or lost under the blanket diagnosis of "sepsis of undetermined origin."

Summary and Conclusions. 1. Prostatic abscess caused by the Friedländer bacillus does not appear to have been previously reported. A case of *B. Friedländer* prostatic abscess is here presented which eventuated in septicemia and multiple metastatic abscesses in the liver, kidneys, lungs and meninges.

2. "Sepsis of undetermined origin" or septicemia with urinary disturbances calls for a thorough investigation of the genito-urinary tract with the possibility of a hidden or masked focus in the prostate to be kept in mind.

3. The scarcity of reported cases of *B. Friedländer* infections of the genito-urinary tract, despite the fact that the bacillus is a more frequent invader of these organs than is commonly thought, is due partly to the existence of many strains of the organism, with mixed infection adding to the difficulty of its identification and, especially, because this organism is still being erroneously associated mainly with respiratory diseases.

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THE TREATMENT OF GONORRHEAL ARTHRITIS WITH ARTIFICIAL FEVER.

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RECENT reports of the remarkable curative effect of artificial fever in the treatment of gonorrheal arthritis suggest that the time is not far distant when this disease will cease to be a serious factor in contributing to the number of the lame, the halt and the disabled. From the standpoint of ultimate joint function and the average duration of discomfort and disability, there is no doubt that the application of this therapeutic principle has greatly improved the outlook of patients with gonorrheal arthritis and that artificial fever constitutes the treatment of choice in such cases. Unusual individual cures have been noted by most workers in this field of therapeutics and these in a high percentage of the cases treated, but relatively little has been said of the failures. Failures there have been and as time goes on and the series lengthens, the results appear a

little less spectacular than they did in preliminary reports. After nearly 2 years' experience we are presenting the results of fever therapy in 50 cases of gonorrheal arthritis. Though the percentage of cures is not so high as has been obtained by other workers, the series is larger than any previously reported and represents the average type of patient with this form of arthritis. By giving a summary of each case in tabular form, it is hoped that the reader may arrive at his own conclusion concerning results in individual cases.

A considerable literature has appeared concerning methods of artificial fever production, the physiologic changes produced by artificial fever and the bactericidal effects of high temperatures on the gonococcus; but this has been fully reviewed in recent papers,^{1,5} so that no attempt will be made to discuss it here. Concerning results of fever therapy in gonorrheal arthritis, Schnabel *et al.*⁶ report 11 cases cured, 5 markedly improved and 2 moderately improved of 18 acute and chronic cases treated. Kendell *et al.*⁴ report: "The ultimate average improvement in joint function in the (19) cases of acute gonorrheal arthritis was 98.4 per cent in the (12) cases of chronic gonorrheal arthritis 88.3 per cent." Hench *et al.*³ report about 90% of their patients (16 cases) were "essentially cured or markedly relieved." These workers tabulated 9 reports from 6 groups of workers published since 1932 on the effect of fever therapy on gonorrheal arthritis. Of 33 cases mentioned, the results of only 24 could be tabulated and of these 22 (92%) were promptly and "completely relieved" or "cured." This tabulation is a composite of four different series of cases; 1 of 12 cases, 1 of 8 and 2 cases each. Such short series have the essence of preliminary reports and their reduction to statistical averages introduces the probability of considerable error. The expressed opinions concerning fever therapy in gonorrheal arthritis, such as, "Results uniformly successful in acute cases" or "Acts almost as a specific"³ might be modified when tempered with a wider experience.

The material presented in this work consists of 50 cases of gonorrheal arthritis. Of these cases, 41 patients had joint symptoms of 10 weeks' duration or less and are, therefore, considered as acute cases. In 9 other patients, classified here as cases of chronic gonorrheal arthritis, the joint symptoms had been present for 4 months or longer. This arbitrary separation may be open to criticism, but patients in the latter group differed materially from the acute cases in that swelling was absent and pain was much more mild and even intermittent. All but 1 patient had symptoms dominated by tender heels, resulting from an inflammation of the posterior attachment of the plantar fascia. This process often interferes with locomotion and, therefore, is confused with a true arthritis of the ankles. It is seen only as a sequela of gonorrhea and often persists long after the original infection has subsided or has been cured.

The diagnosis of gonorrheal arthritis in our patients was made

by a critical consideration of the history, course and bacteriologic evidence of gonorrheal infection of the genital system and the character and type of joint disease. Classically, this occurs as a sudden, severe, extremely painful arthritis involving usually one joint and leading to rapid bone and cartilage destruction and tendon sheath inflammation. Formation of adhesions and thickening of the joint capsule result in marked limitation of joint motion or ankylosis. While such a sequence of events is suggestive of gonorrheal arthritis, it is by no means pathognomonic of this disease as the same syndrome is often seen in patients who exhibit neither suspicion nor evidence of gonorrhea. On the other hand, patients with histories of recent gonorrheal infection may have a mild migratory arthritis, limited after a short time to one joint which develops effusion, showing many pus cells and Gram-negative intracellular diplococci. A diagnosis of gonorrheal arthritis can be made with certainty only when the specific organisms are found by smear or culture in the affected joints.

According to such criteria, only 3 of this series of patients had gonococcal arthritis proven by joint culture. Of the patients with acute arthritis, all but 5 had positive urethral, prostatic or cervical smears before treatment. Three of these showed joint fluid from which gonococci were cultured (R. K., D. A. and H. B.). One of the others (M. S.) had been treated repeatedly for gonorrhea and had a urethral discharge for several days prior to the onset of arthritis. The last case (M. M.) gave a history of vaginal discharge for 4 weeks. When seen, this discharge showed many pus cells, but Gram-negative intracellular diplococci were not identified in it. The diagnosis of gonorrheal arthritis may be open to question but seemed justified on an examination of all the evidence.

Of the patients with chronic joint symptoms, only 1 had a positive smear when seen by us, but all gave definite histories of acute gonorrhea which had been adequately treated elsewhere and pronounced cured. Painful heels or arthritis had persisted since the infection. Roentgen ray films were taken in only 1 case which showed calcaneal spurs.

Apparatus and Procedure. All fever treatments were given by means of the Kettering hypertherm,* which consists of a cabinet large enough to accommodate comfortably the body of a man. The patient lies upon an air mattress resting on a built-in cart which can be withdrawn. This arrangement facilitates putting the patient into the cabinet and allows for his rapid withdrawal, if necessary. The patient's head rests upon a pillow outside the cabinet, the end of which is closed by means of a vertically sliding door. A large sliding door on each side allows for easy examination of the patient's body during the treatment, the taking of rectal temperatures and the changing of blankets which are placed over the body during part of the treatment. A compartment at the foot of the cabinet contains electrical apparatus which heats and humidifies the air and causes it to

* The Kettering hypertherm cabinets were loaned to City Hospital for clinical trial through the generosity of Mr. C. F. Kettering, President of General Motors Research Corporation, Dr. W. M. Simpson, of the Miami Valley Hospital, Dayton, Ohio, and the Frigidaire Corporation, Dayton, Ohio.

circulate. The air temperature and humidity are controlled automatically at any desired level.

The patient comes to the fever therapy department about 8 A.M. without breakfast and, after the temperature, pulse, blood pressure and weight are recorded, he receives sodium amytal (gr. vj). He then enters the cabinet nude save two boots made of several layers of outing flannel which cover the feet and lower parts of the legs, areas which are especially liable to blister. The air temperature in the cabinet at the beginning of the treatment is about 125° F. and is raised as rapidly as possible to 160° F. The humidity is maintained at about 35%. After about 1½ hours, the desired body temperature is produced and the patient is then covered with a blanket. From this time forth the cabinet air temperature is adjusted as necessary to maintain the desired fever. An electric fan plays on the patient's face, iced water or iced saline is given freely and the patient may eat ice or have ice rubbed on his face. Morphine is given hypodermically for undue discomfort or restlessness. A nurse is in constant attendance to regulate the treatment and to minister to the patient's wants. She observes and records the patient's temperature, pulse and general behavior as well as the air temperature and humidity of the cabinet at least every 15 minutes. The condition of the skin is noted to detect inflamed areas which might later develop into blisters. The nurse attends to but 1 patient at a time, and upon her intelligence, tact and judgment depends to a large extent the success of a treatment. When the treatment is terminated, the cart with the patient on it is withdrawn from the cabinet and after 1 or 2 hours the body temperature returns to the pre-treatment level. After a bath the patient is returned to the ward or may be taken home.

An attempt is made at each treatment to maintain a fever of 106° to 107° F. for at least 5 hours. If this elevation is attained rapidly, the patient is reasonably comfortable and there is no evidence of skin blisters; the period is extended to 6 or 7 hours. At the end of such a fever, patients with gonorrheal arthritis usually feel greatly improved. Pain and tenderness is markedly reduced and the range of joint motion is increased. If symptoms are not absent or do not continue to improve, fever treatments are repeated every 3 to 6 days, if possible, as long as improvement is noted. This routine is frequently disturbed and successive treatments delayed because of skin burns and blisters or painful and extensive herpes.

An important part of the patient's preparation for treatment consists in describing and explaining the procedure to him. He is told that the treatment will probably give him relief of this arthritis and his infection may possibly be cured. It is explained that the treatment is long and tedious, that the cabinet is very hot and uncomfortable, that he may suffer skin blisters and herpes, but that everything in the way of drugs and attention will be allowed to make it as easy for him as possible and that we believe he can tolerate it. Practically no one has hesitated to submit to treatment, while the few who have refused to continue have done so without resentment.

Because of the high temperatures and long treatments necessary, fever therapy in gonorrhea is much more difficult than in chronic arthritis, central nervous system lues, inflammatory eye conditions or other conditions for which it seems to be of benefit. The nervous and mental strain on the patient, the tendency to skin lesions due to thermic injury, the liability to encounter uncontrolled hyperpyrexia or circulatory collapse is increased as the temperature level is elevated.

RESULTS. So far as possible, the significant data are presented in four tables. The cases in each table are listed in order of increasing duration of arthritic symptoms. No record is stated as to the number of fever treatments given, but this may be estimated by

considering that each treatment lasts from 4 to 6 hours. The actual duration of a treatment is much longer, since the period of temperature rise is not included. Treatments are listed as "hours above 105° F." because of the difficulty at times in raising the fever to 106° F. or in keeping it there without interruption. The actual period and temperature of treatments exceed rather than fall short of the time as given. In most cases the temperature was kept as close to 107° F. as was thought to be safe.

Table 1 shows the data on 22 patients who received complete relief or cure of all joint symptoms. This means that they were free of pain and tenderness; the joints looked normal and were able to perform satisfactorily all the motions necessary in the patient's usual activity without attracting notice of an observer, although

TABLE 1.—ACUTE GONORRHEAL ARTHRITIS WITH COMPLETE RECOVERY.

	Sex.	Age.	Smear before treatment.	Duration.		Involve-ment.	Fever of 105° F. hr.	Remarks.
				Gon.	Arth.			
J. T.	F	22	+	1 yr.	1 wk.	Wrist	12	Pus tubes removed surgically after treatment; smear neg.
A. P.	M	30	+	1 "	1 "	Knee	8	Smear negative.
M. S.	M	37	—	2 "	1 "	Knee	5	History of repeated gonorrhea; urethritis recently; knee aspirated of 70 cc. of fluid.
W. R.	M	40	+	2 "	1 "	Knee	30	Conjunctivitis promptly relieved; smear neg.
M. K.	M	42	+	5 wk.	2 "	Ankle	5	Smear not obtainable.
J. M.	M	30	+	3 "	2 "	Elbows	20	Smear negative.
J. M.	M	40	+	3 "	2 "	Knee	5	Knees tapped twice; showed Gram-neg. dip. but none intracellular.
J. B.	F	23	+	?	2 "	Knee	5	
E. W.	M	44	+	12 wk.	2 "	Wrist	10	Conjunctivitis promptly relieved.
R. S.	M	20	+	18 "	3 "	Ankles	5	
F. S.	M	38	+	?	3 "	Knee	10	Smear negative.
C. W.	M	36	+	4 wk.	3 "	Wrist	5	
B. B.	F	42	+	None	3 "	Hip	5	Roentgen ray showed joint destruction.
W. D.	M	49	+	4 wk.	3 "	Knee	10	Conjunctivitis promptly relieved.
J. O.	M	22	+	8 "	3 "	Wrist	9	Periurethral abscess; smears became neg.
D. T.	F	24	+	4 "	3 wk.	Heel	15	
B. M.	M	32	+	1 yr.	4 "	Knee	10	
C. G.	M	21	+	4 wk.	4 "	Hip	16	
J. P.	M	22	+	8 "	4 "	Ankles	7	
T. D.	M	20	+	7 "	6 "	Toes	5	
A. L.	F	5	+	?	7 "	Knee	7	Gonococcic vaginitis; Roentgen ray showed epiphyseal destruction; normal 5 wk. later.
G. L.	M	26	+	?	8 "	Wrist	13	Roentgen ray shows haziness.

full anatomic motion was not always restored. One patient of special interest, but 5 years of age, had a gonorrheal vaginitis and a very tender, swollen and immovable forefinger which had been present for 6 weeks. A Roentgen ray photograph before treatment showed almost complete disappearance of the epiphysis of the proximal end of the first phalanx, whereas 5 weeks later the epiphysis was normal.

Table 2 includes 9 patients who received benefit but were not cured. In general, these patients had suffered from arthritis for

TABLE 2.—ACUTE GONORRHEAL ARTHRITIS WITH PARTIAL RELIEF.

	Sex.	Age.	Smear before treatment.	Duration.		Involve-ment.	Fever of 105° F.	Remarks.
				Gon.	Arth.			
K. S.	F	29	+	1 yr.	1 da.	Hip	48	First treatment within 24 hr. of first pain; developed joint damage by Roentgen ray under treatment; treatment continued for cure of infection; result: painless joint motion from complete extension to 90 degrees flexion.
A. G.	M	25	+	4 wk.	3 wk.	Foot	5	Roentgen ray showed destruction; treatment stopped for uncontrolled hyperpyrexia; foot slightly tender.
M. M.	F	16	—	16 "	3 "	Hip	20	Vaginal discharge, 4 wk.; smear: much pus, no definite gonoc.; Roentgen ray before treatment: haziness and narrowed joint space; kept in bed 4 wk. after relief of joint pain for recalcification; motion, 180 to 90 deg.; walked with slight limp.
V. S.	M	27	+	6 "	5 "	Ankles Heels	40	Gonoc. iritis promptly relieved; ankle cured; one heel tender.
L. S.	M	28	+	10 "	6 "	Ankles Wrist	29	Wrist cured; one ankle slightly tender.
W. B.	M	30	+	Denied	6 "	Wrist Hand	32	Roentgen ray before treatment showed joint destruction; complete relief of pain and tenderness.
C. R.	F	19	+	10 wk.	6 "	Knee Hip	10	Roentgen ray showed destruction before treatment; complete relief of pain and tenderness; partial motion of hip, normal of knee.
W. R.	M	..	+	9 "	7 "	Foot	7	Severe pain relieved; slight residual tenderness.
R. K.	M	23	—	10 "	8 "	Knee	8	Joint culture positive; pain had subsided; before treatment, motion nil, after 180 to 90 deg.

a longer time when treated than did those in the previous group. The significance of this delay is suggested by the fact that 4 patients showed Roentgen ray signs of joint damage before fever therapy was employed. That prompt fever treatment does not always protect against joint damage is illustrated by the first patient (K. S.). The onset of her arthritis was quite sudden and very painful and she had her first fever treatment, 5 hours about 106° F., within 24 hours of the first joint symptom. She had only partial relief of pain. The second treatment had to be delayed 13 days because of burns. Fever treatments in this case were continued after the joint condition became stationary in a successful effort to render her cervical smears negative for gonococci.

One patient (W. B.) showed definite destruction of bones of the wrist by Roentgen ray and had incision and drainage of suppurating tendon sheaths of the wrist before treatment. The wrist, hand and fingers were extremely tender and immovable. Fever therapy relieved the pain and tenderness completely and he regained partial mobility of the wrist, hand and fingers. This is all that could possibly be expected from any treatment, perhaps, under the circum-

TABLE 3.—ACUTE GONORRHEAL ARTHRITIS WITH DOUBTFUL RELIEF.

	Sex.	Age.	Smear before treatment.	Duration of arthritis	Involve-ment.	Fever of 105° F.	Remarks.
D. A.	F	18	—	1 wk.	Knee	15	Joint culture positive; Roentgen ray before showed damage; relief of pain and tenderness; motion limited to 30 degrees.
J. B.	M	..	+	1 "	Knee	6	No relief; refused further treatment.
R. S.	M	34	+	2 "	Knee	6	No relief; refused further treatment.
A. K.	F	28	+	2 "	Wrist	15	Tenderness and swelling relieved; Roentgen ray before treatment negative 1 month later; severe demineralization.
L. J.	F	43	+	2 "	Knee	15	Gradual relief of pain and tenderness.
C. L.	M	17	+	2 "	Wrist	13	Gradual relief of pain and tenderness but motion limited; developed Roentgen ray destruction under treatment.
B. K.	M	23	+	4 "	Knee	10	Refused further treatment.
J. B.	M	55	—	6 "	Hand Ankle Knee	30	Gradual relief of pain and tenderness; joint culture was positive; Roentgen ray destruction under treatment.
L. W.	M	44	+	7 "	Knee Ankle	3	Treatment discontinued because of circulatory collapse; further treatments not given.

stances. In 3 cases (K. S., C. R. and M. M.) the severity of the joint symptoms and Roentgen ray appearance suggested that bony ankylosis was to be expected, but all the patients were discharged with painless movable joints for which fever therapy seems responsible. Four patients (V. S., L. S., W. R., and A. G.) noted relief of severe pain but continued to suffer moderate and prolonged tenderness with definite limitation of motion which further fever therapy did not relieve. R. K. had marked improvement in function which further treatment might have increased but he insisted on his discharge.

Table 3 includes 10 patients who received no benefit from fever therapy. Though several of these patients showed some improvement under our observation, this was so slight in amount and so slow in appearance that it can be explained satisfactorily as the natural evolution of the disease. In contrast to the general experience, these patients noted little or no relief of pain during or directly after fever therapy. In only 2 cases (D. A. and L. J.) was there Roentgen ray evidence of joint damage prior to fever treatment, while 4 (A. K., C. L., H. D. and M. I.) developed such damage after fever therapy was started. Five patients were inadequately treated because they refused further treatment or because their reaction under therapy made further treatment seem inadvisable.

Table 4 includes 9 patients suffering with chronic manifestations of gonorrheal joint disease. The members of this group differed materially from those previously discussed. Acute pain had long since passed or had never been prominent, the joint symptoms were dominated by intermittent soreness or tenderness often relieved by exercise and without evidence of joint damage. Eight of these patients noted tenderness at the point of the heel which made walk-

TABLE 4.—CHRONIC GONORRHEAL ARTHRITIS.

	Sex.	Age.	Smear before treatment.	Duration of arthritis.	Involve-ment.	Fever of 105° F.	Remarks.
M. M.	M	..	—	4 mo.	Heels Ankle Hip	12	Roentgen ray shows spurs; partial relief; heels remain slightly tender.
W. C.	M	..	0	4 "	Heels	5	Complete relief.
J. K.	M	..	0	7 "	Heel	2	Complete relief.
J. S.	M	..	±	11 "	Ankle Heels	3	Complete relief.
W. W.	M	..	0	12 "	Heels	5	Complete relief.
W. B.	M	..	0	12 "	Heels	13	Partial relief.
W. P.	M	..	0	18 "	Heels	5	Partial relief.
J. G.	M	..	0	24 "	Knees	10	No benefit.
W. G.	M	..	0	24 "	Ankles Heels	1	Partial relief; stopped treatment because of extreme discomfort.

ing very difficult at times. Four patients had complete relief with a single treatment and 1 nearly complete. The latter patient was treated recently and will have further therapy. Substantial benefit was seen in another patient who suffered severe abdominal cramps during fever treatment which had to be discontinued after 1 hour of fever. Two other patients received only partial help with what was considered adequate therapy. One patient received no benefit.

Amount of Fever Therapy. A considerable variation is noted in the number of hours of fever which the patients received since some responded more rapidly than others. The longest duration of fever in a patient in Table 1 was 30 hours. Eight patients in this group required only 5 hours for complete relief and the average for the group was about 10. Of the group with partial relief, 1 patient received 48 hours of fever therapy. This was about twice as much as was indicated for joint symptoms, but treatment was continued until cervical smears became negative. The average treatment for this group was 21 hours, twice as much as in the previous one. The third group, which noted little, if any, relief, received an average of 12 hours, a figure notably reduced by the number of patients who refused further treatment or whom we preferred to discontinue. The group of chronic patients had an average of about 6 hours of fever. Treatment of 3 of these patients had to be discontinued (J. K. after 2 hours because of delirium, due to sodium amytal, J. S. after 3 hours because of persistently high pulse, and W. G. because of abdominal cramps). Despite such short treatments the first 2 of these patients received complete relief and the third partial relief. In successful cases it appears that tender heels may be relieved by fevers of short duration.

Effect on Other Symptoms. No routine attempt was made to cure the genital infection in arthritic patients. At the beginning of our experience with but one cabinet available, the press of new patients was so great that we did not feel justified in attempting to cure the genital lesion. Now with greater capacity, it is found that relatively few of our patients wish to submit to further treatments after the arthritic symptoms have subsided. Inasmuch as arthritis has been our main consideration, there has been no great pressure brought to bear on the patients. In 5 cases, definite efforts were made to effect a bacteriologic cure of the genital infection. In 1 case of arthritis, cervical smears became negative after 48 hours of fever and remained so during a 2 months' period. This patient also had tender masses on pelvic examination which disappeared. Two men without joint symptoms, 1 with prostatitis and urethritis and 1 with prostatitis and epididymitis were cured of all symptoms and discharged; shreds disappeared from the urine and prostatic smears showed only occasional pus cells without organisms during a period of 3 and 5 months that they were followed after treatment. The first patient had 15 hours of fever in 3 treat-

ments, the other 6 hours in 1 treatment. Another patient with urethritis and epididymitis received symptomatic relief and had negative smears after 10 hours of fever in 2 treatments. He unfortunately was not followed. One woman still had positive cervical smears after 40 hours of fever of about 106° F. Treatment of another patient with urethritis and epididymitis was discontinued after 1 hour because of delirium and circulatory collapse.

Of the series of arthritics, 4 had gonorrheal conjunctivitis and 1 had iritis. These conditions were relieved in every case during fever treatment for arthritis. The pain, swelling and injection usually disappeared promptly and the discharge subsided after several treatments. These patients escaped without corneal opacities. The patient with iritis was promptly relieved and now has no ocular symptoms, although adhesions did persist which are evident only after dilatation of the pupil with atropin.

COMPLICATIONS. Because of the severity of the treatments used, the hazards, complications and accidents encountered in the fever treatment of gonorrhea are much more common and serious than those seen in the treatment of other conditions. The patient requires larger doses of sedatives. Cyanosis occasionally develops from the use of morphin, but this is localized to the head and neck which are outside of the cabinet, the rest of the body retaining the deep flush so consistently present. Cyanosis occurs only when the patient dozes off to sleep and is promptly relieved by awakening him. The most serious effect of overdosage with morphin is diminished pulmonary ventilation, which seems to be adequately counterbalanced by the respiratory stimulation caused by heating the skin. Such respiratory stimulation at times induces sufficient hyperventilation to cause alkalosis and tetany. This occurs shortly after the patient enters the cabinet and is still without blanket covering. It is manifest by numbness and tingling of the hands and fingers and rarely by carpopedal spasm. Relief is obtained in a few minutes by lowering the cabinet air temperature slightly. Calcium gluconate intravenously is very promptly effective.

Occasionally, patients are encountered who become delirious, hyperactive or even maniacal from sodium amytal. Six grains is usually given before treatment. Inasmuch as this seems at times to be an exciting dose, an additional 3 grains is often beneficial for restlessness. If the patient becomes more restless and thrashes around in the cabinet, his temperature promptly rises to a higher level. With a temperature of 106.5° to 107° F. very little muscular activity is sufficient to produce an alarming fever in a very short time. With this additional fever deep coma may ensue, associated with a very rapid pulse, 180 to 200, a profound fall in peripheral blood pressure and a condition which appears similar to profound surgical shock save for the extreme warmth of the skin. Caffein sodium benzoate, adrenalin and 50 cc. of 50% glucose solution

intravenously cause a rise in blood pressure and slowing of the pulse. The patient gradually recovers consciousness as the temperature falls. Mild disorientation, extreme lassitude and severe headache followed later by nausea may ensue for 6 to 24 hours. Dehydration is severe and is partly due to vomiting.

The most serious experience of this kind occurred while treating a patient with prostatitis and epididymitis. The sequence of events was about as described above, except that he remained mildly disoriented and complained of a severe headache. His blood pressure varied between 60 and 80 mm. Hg. Six hours after removal from the cabinet he had a severe epileptiform seizure for about 10 minutes following which he was noted to have a facial paralysis and aphasia, which completely disappeared in about 2 weeks. Two other patients suffered similar complications in milder form, neither showing evidence of organic cerebral complications. Further fever therapy was not attempted on these patients. Two other individual treatments were discontinued because of sodium amytal delirium, but the patients later had satisfactory sessions.

It seems remarkable that the delirium of fever which is frequently seen in diseases at much lower temperatures is so rarely encountered in patients receiving artificial fever therapy. Many patients exhibit a very delicate limit of fever, varying from individual to individual, beyond which they become definitely disoriented. For example, we had 1 patient who maintained a perfectly clear sensorium at 106.8° F., but who became disoriented when the temperature rose to 107.2° F. Indeed, some patients may become disoriented with temperatures as low as 105.8° F. A few patients have remained lucid for considerable periods, from 15 to 30 minutes, at 107.5° F. We have been unable regularly to maintain the fever at such a constant level as has been described in other reports.

The ability of a patient to tolerate a definite level of fever seems to be inherent and fixed without evidence that it is increased by practice or decreased by fatigue. Individual patients have demonstrated the tolerance for fever at the same level on repeated treatments. It seems significant, also, that the patients who collapsed did so at their first treatment before or just as the desired temperature level was reached. A definite opinion has been formed by members of the department, based on experience, that if all is well by 11 A.M., no trouble is to be encountered that day.

Skin burns and blisters occur in a considerable number of patients in spite of the fact that the Kettering hypertherm contains no contact coils, electrodes or heating elements in the cabinet proper with which it is possible for any part of the patient's body to come in contact. These are the result of thermic injury of the skin due to hot air. This is not so surprising as one might think for air temperatures of 150° F. or higher may have to be maintained for 6 or 7 hours during some treatments. Certain patients tolerate this

exposure without difficulty but others, particularly those with delicately textured and fair complexioned skins, develop an intense erythema which later becomes mottled with white or ischemic areas. As such areas appear, they are massaged or kneaded gently and protected with extra pads in an effort to avert blister formation, and when such seem imminent, the treatment is terminated. Not infrequently blisters do not become evident until the following day. Patients with gonorrhea are warned of the possibility of burning as such accidents occur in about one-third of the patients.

As a rule, burns are only of the first degree and heal without scars, but it is desirable to avoid them for they necessitate curtailing the treatment or delaying the following one. Certain areas of the skin are particularly prone to blister. The toes, feet and lower legs are protected at all times by outing flannel boots and, therefore, cause very little trouble. Skin, where it is stretched over bony prominences such as the anterior-superior spines of the ilia and lower border of the ribs, is especially vulnerable as is that covering abdominal scars or pendulous breasts. Other parts where burns develop include the anteromedial aspects of the thighs, across the upper chest and the anterior aspects of the upper arms.

Herpes labialis develops in about one-third of the patients and frequently is extensive, involving the lips and skin about the mouth and chin, the labial portion of the buccal mucosa but rarely the mucosa of the hard palate. It usually becomes evident from the third to the fifth day following therapy, lasts about 5 days, invariably heals without leaving scars and occurs only after the first treatment.

The most common difficulty of patients with gonorrhea after fever treatments include nausea, vomiting and anorexia. Most patients notice nausea directly after treatment which may persist for 12 to 24 hours. Vomiting may occur upon removal from the cabinet, but usually is delayed until the patient is moved to the ward or gets up to go home. It may occur after supper if this is attempted on the treatment day. Occasionally patients are hungry and eat well at supper time, but many lack all interest in food until the following noon. They are urged to eat as soon as they feel a desire for food.

RATIONALE. The effectiveness of high temperatures as a gonococcicide has long been recognized and innumerable examples of the curative effects of severe fever from spontaneous disease upon preëxisting gonococcal infections have been reported in the literature.^{5,7} It remained for the work of Carpenter^{5,8} and his associates to demonstrate laboratory confirmation of this observed clinical fact. By *in vitro* experiments with 130 different strains of gonococci, they found it required from 6 to 27 hours in an incubator at 106.5° F. for complete sterilization of the various cultures. They noted further that slight reductions in incubator temperatures

resulted in a marked increase in the time required for sterilization. They have evidence to suggest that the gonococcus becomes more heat-resistant with repeated non-lethal exposure to high temperatures. These workers report that 11 patients with gonorrhea, who were given a single fever treatment of 106.5° F. maintained for a period equal to the thermal death time of their particular strain of the gonococcus, noted an immediate subsidence of all symptoms and had a bacteriologic cure. The fact that 9 other patients noted similar results with fever treatment of from one-fourth to three-fourths of the thermal death time suggests that bodily mechanisms of defense often are called into action to produce a cure.

In view of the above facts, a study of the cases here reported indicates that it is extremely unlikely that the thermal death time was equalled in many cases, even though joint symptoms were controlled. In only a few cases does it seem likely that the genital focus of infection was cured. This suggests that metastatic gonorrheal infection in joints is more vulnerable to sterilization from direct heat or defense mechanisms of the body than is the primary genital infection.

In attempting to analyze the value of artificial fever in the treatment of gonorrheal arthritis, reference must be made to the expectancy of spontaneous remission in the disease. We are not aware of statistical studies on this subject, but we are convinced that a significant proportion of cases attain a satisfactory result without medical intervention. We have no idea what this proportion may be. Anyone familiar with this disease can recall even severe cases which recovered following only bed rest or joint protection during the acute stage. In a study of synovial fluid, Myers *et al.*⁹ state that 25% of 33 patients became well following gonococcal arthritis and noted a direct relationship between prognosis and cell count of the synovial fluid. These cases were of sufficient severity to have fluid in the joints which could be removed by tapping. No mention is made of the therapy employed.

The experiences recorded in this paper have convinced the authors that fever therapy constitutes a practical, safe and satisfactory method of treatment in gonorrheal arthritis, producing cure or relief for a high percentage of patients treated and reducing markedly the period of disability and discomfort attendant with this disease. The treatment is highly technical and not to be undertaken without careful supervision by a trained personnel. It is not without hazard and disagreeable complications seem unavoidable.

Summary. Fifty cases of gonorrheal arthritis, treated with artificial fever (105° to 107° F. from 1 to 48 hours) in the Kettering hypertherm are reported. Of these patients, 26 (54%) were relieved of all joint symptoms, 11 (22%) received benefit, while 13 (26%) were not helped. The apparatus and procedures are described in detail, mention is made of the common complications encountered. The rationale of fever therapy in gonorrheal arthritis is discussed.

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**THE EFFECT OF INTRAVENOUS INJECTIONS OF SUCROSE
SOLUTION (50%) ON THE CEREBROSPINAL FLUID PRES-
SURE, THE BLOOD PRESSURE AND CLINICAL COURSE
IN CASES OF CHRONIC HYPERTENSION.***

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THE relationship between arterial hypertension and increased cerebrospinal fluid pressure has been noted by many investigators since Traube's observations in the year 1871.¹ Yet a review of the literature on the subject up to recent times shows that there was no unanimity of opinion concerning the correspondence of the pressure changes in the two systems. Recently, however, Shelburne, Blain, and O'Hare² have pointed out that there is an almost constant association between an excessively high diastolic blood pressure, and an increase in the spinal fluid pressure. They have shown further that there is a relationship between the cerebrospinal fluid pressure, a high diastolic blood pressure, and papilledema. They found in-

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creased intracranial pressure more often associated with high diastolic blood pressure but felt that both were probably the results of some common factor, neither caused by the other. The results of their study were in harmony with those published later by Pickering.³ He concluded that there is a relationship between high diastolic blood pressure and high cerebrospinal fluid pressure and suggested that the former is one of the factors determining the latter.

From clinical observations it may be concluded that in patients with excessively high blood pressures the most aggravating symptoms often refractory to treatment are those not of renal failure, but of edema of the brain and increased intracranial pressure. The headache, nausea and vomiting, vertigo, and the disturbances of vision associated with papilledema are evidences of increased intracranial pressure and are often the prodromes of convulsive seizures. In such cases spinal fluid pressure is usually considerably elevated and commonly the diastolic blood pressure is 130 mm. of Hg. or above. Autopsies in such cases show the brain is edematous, pale, and bloodless. Although there are other theories concerning the production of these symptoms Volhard⁴ prefers to consider edema of the brain as the most important factor.

For the relief of intracranial pressure of nephritis and of hypertension, several methods have been employed. For example, in 1908, Cushing and Bordley⁵ performed subtemporal decompression in such cases for the reduction of cerebrospinal fluid pressure. They noted marked improvement in the general condition of the patient and particularly an improvement in the visual acuity. Lumbar puncture has been used for relief of symptoms but it has been shown by Shelburne, Blain, and O'Hare,² and by such authors as Volhard⁴ and Blackfan and Hamilton⁶ that serious unfavorable results may follow spinal puncture. The release of the pressure may cause the medulla oblongata to become pressed into the foramen magnum and lead to respiratory failure and death.

When it was discovered experimentally by Weed and McKibben,⁷ in 1919, that hypertonic salt solution and hypertonic glucose solution given intravenously would cause a reduction of brain fluid volume and spinal fluid pressure, the clinical application of this discovery soon followed. The first clinical report was made by Haden⁸ who used a 40% solution of glucose for the treatment of intracranial pressure in cases of meningitis. The results were favorable. The value of these hypertonic solutions was more greatly appreciated by surgeons than by internists and their chief clinical use has been in the field of surgery in the treatment of increased intracranial pressure produced by acute and chronic lesions within the cranial cavity itself.

Hypertonic saline solutions were shown to reduce spinal fluid pressure but later were found to be toxic by Browder⁹ who claimed there was danger in the use of them. Blackfan and Hamilton⁶

employed magnesium sulphate for the reduction of intracranial pressure. Fay¹⁰ advocated giving magnesium sulphate by mouth for the same purpose in treating patients with intracranial lesions. Hypertonic glucose solution has been widely used and advocated for this purpose, especially by Peet¹¹ who used intravenously 50% solution daily. The value of hypertonic glucose solution in such cases has been questioned by several authors among whom are Milles and Hurwitz,¹² Jackson, Kutsunai, Leader and Joseph.¹³ In their opinions the reduction of cerebrospinal fluid pressure with hypertonic glucose solution is transient and within a period of 3 hours a secondary rise above the basic level occurs. They concluded that the use of such a measure carries an obvious danger.

Bullock, Gregersen and Kinney,¹⁴ in an experimental study, compared the effects of intravenously injected glucose, sodium chlorid, and sucrose upon the cerebrospinal fluid pressure. They found that the intravenous injection of 50% glucose solution and 30% sodium chlorid reduced the spinal fluid pressure for 2 to 3 hours; the pressure then rose above the control level. Hypertonic (50%) sucrose injected intravenously reduced the spinal fluid pressure in dogs for from 5 to 8 hours without causing a secondary rise exceeding the initial pressure. They explain that this effect is because of the increased osmotic pressure of the blood. It remains in the blood longer than glucose or sodium chlorid solutions and has a more prolonged effect because it is not broken down or utilized as is glucose nor on the other hand is it stored in the tissues as is sodium chlorid. Pronounced diuresis follows sucrose injections and this eliminates the sucrose as well as fluid withdrawn from the tissues. The excretion and utilization of sucrose when injected intravenously were studied by Keith and his associates.¹⁵ They found that in normal persons 97 to 98% of sucrose was excreted in the urine in 24 hours. In contrast to the rapid excretion of sucrose by the normal person, they found that in patients with renal insufficiency there was a delay in excretion. In spite of the delay the total amount recovered was 88 to 99%.

Recently Masserman¹⁶ presented evidence to show that when hypertonic solution of glucose in effective amount and concentration is given intravenously for the purpose of reducing intracranial pressure the reduction of cerebrospinal fluid pressure may be followed by a period of increased intracranial pressure and by a number of unfavorable signs and symptoms. In an attempt to find a non-toxic substance whose osmotic action would not be complicated by these unfavorable sequelæ he investigated the effects of intravenous hypertonic solution of sucrose. He concluded that a 50% solution of sucrose was satisfactory for clinical use and that as high as 500 cc. of this solution may be given intravenously without any toxic or other untoward symptoms. The desired reduction in intracranial pressure was obtained and the effect was greater and more prolonged than that of glucose solution. Masserman noted that a

marked diuresis followed the use of sucrose solution. He suggested the use of this measure to reduce intracranial hypertension in medical and surgical cases.

Clinical Observations. With these observations on cerebrospinal fluid pressures in hypertensives in mind, and in view of the favorable effects of hypertonic sucrose solution in other types of cases, we were led to attempt to obtain temporary relief of symptoms of intracranial pressure of hypertensives by daily intravenous injections of hypertonic sucrose solution. The purpose of this report is to present the effects of giving patients with hypertension 50% sucrose solution intravenously. Especial attention is given to the influence of the injections upon the spinal fluid pressure, blood pressure, eye-ground changes, and the clinical course of the disease. In all, 21 cases of hypertension were selected: 10 had essential benign hypertension, 7 had malignant hypertension, and 4 were cases of chronic glomerular nephritis. Spinal fluid pressure readings were made with an Ayer water manometer. A reading of less than 200 mm. was considered normal.

TABLE 1.—CLINICAL DATA IN 10 CASES OF BENIGN HYPERTENSION.

Case.	Age, yrs.	Blood pressure, mm. Hg.	CSF pressure, mm. water.	Papill- edema.	Renal failure.	Cardiac failure.
1	48	190/100	125	0	Mild	Advanced
2	38	180/116	90	0	0	Moderate
3	57	200/110	215	0	0	Mild
4	44	200/145	205	+	Mild	Advanced
5	30	196/134	250	0	0	Mild
6	53	230/100	250	0	Mild	Advanced
7	28	240/116	130	0	Severe	Advanced
8	49	224/120	185	0	0	0
9	51	210/125	178	0	0	Mild
10	48	215/110	195	0	0	0

In Table 1 the clinical features of the group of benign hypertensives are tabulated. It is seen that no decided increase in intraspinal pressure was present in most cases. Exceptions, however, are seen in Cases 5 and 6. Although the diastolic blood pressures and cerebrospinal fluid pressures are elevated, no papilledema was found. These cases show that no constant relationship exists between high diastolic blood pressure and increased cerebrospinal fluid pressure.

TABLE 2.—CLINICAL DATA IN 7 CASES OF MALIGNANT HYPERTENSION AND IN 4 CASES OF CHRONIC GLOMERULAR NEPHRITIS.

Case.	Age, yrs.	Diagnosis.	Blood pressure, mm. Hg.	CSF pressure, mm. water.	Papill- edema.	Renal failure.	Cardiac failure.
11	37	Malig. hyper.	200/140	350	++	Advanced	Advanced
12	56	Malig. hyper.	200/130	250	++	Mild	Advanced
13	43	Malig. hyper.	250/140	250	++	Mild	Advanced
14	48	Malig. hyper.	182/120	275	++	Moderate	Advanced
15	45	Premalig. hyper.	210/125	350	0	Moderate	Moderate
16	39	Malig. hyper.	230/190	200	++	Advanced	Advanced
17	58	Malig. hyper.	260/140	200	++	Mild	Advanced
18	40	Chr. glom. nephr.	240/150	150	++	Advanced	Advanced
19	30	Chr. glom. nephr.	180/110	250	++	Advanced	0
20	28	Chr. glom. nephr.	180/100	200	++	Advanced	Advanced
21	38	Chr. glom. nephr.	210/150	350	++	Advanced	Mild

In Table 2 are placed the cases of malignant hypertension and of chronic glomerular nephritis. With few exceptions there is a decided increase in cerebrospinal fluid pressure. The high diastolic blood pressure and renal failure seem to correspond to the elevation of spinal fluid pressure and papilledema. An exact correspondence, however, is lacking as seen in Case 15 where no papilledema is present although the spinal fluid pressure is 350 mm. of water. By the exceptions in these cases it is evident that there is no constant relationship between diastolic blood pressure and increased cerebrospinal pressure, for diastolic pressure may be constantly elevated yet there is no increase of spinal fluid pressure.

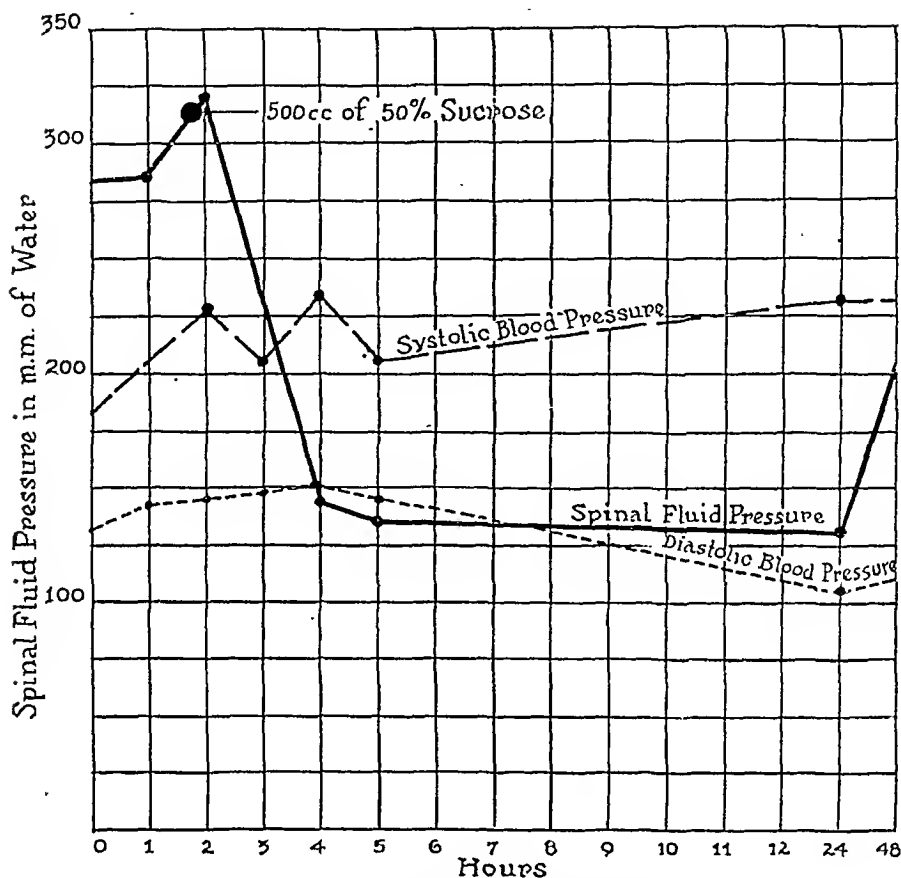
TABLE 3.—SUMMARY OF DATA SHOWING THE CORRELATION BETWEEN ARTERIAL HYPERTENSION AND INCREASED CEREBROSPINAL FLUID PRESSURE.

No. of cases.	Average systolic blood pressure, mm. Hg.	Average diastolic blood pressure, mm. Hg.	CSF pressure.	Number systolic above 220.	Number diastolic above 130.
7	214	112.9	Below 200 mm. water	3 (43%)	1 (14.9%)
14	210	131.0	Above 200 mm. water	4 (28%)	7 (50%)

Referring to Table 3 a summary is given showing the correlation between the elevation of cerebrospinal pressures and high diastolic blood pressures. Of 14 cases with spinal fluid pressure of 200 mm. of water and above, 7 had a diastolic blood pressure of 130 mm. of Hg. or above. Of 7 patients with cerebrospinal fluid pressure below 200 mm. of water, 1 (14.9%) had a diastolic blood pressure above 130 mm. of Hg. and 3 (43%) had a systolic blood pressure above 220 mm. of Hg. In Case 18 there is a diastolic pressure constantly over 130 mm. of Hg. yet the spinal fluid pressure is normal. The most satisfactory results occur in the treatment of patients with malignant hypertension. The usual response obtained is shown in Graph 1.

Method of Procedure. On the morning of the study, breakfast is withheld and the patient sedated with a drug such as sodium luminal. The mean blood pressure and pulse rates are established by readings every 15 minutes. An indwelling spinal tap needle is placed in the spinal canal and the basic spinal fluid pressure is established. Then the patient is given 300 to 500 cc. of 50% sucrose solution and the blood pressure, spinal fluid pressure, and pulse rates are followed every 15 minutes. This procedure is carried on as long as the patient is able to tolerate comfortably the indwelling spinal tap needle; this is a period usually from 2 to 5 hours. When the solution is given to patients with benign hypertension the spinal fluid pressure drops from 80 to 100 mm. below the basic level. Within 5 to 12 hours it gradually returns to normal. No unfavorable symptoms develop, such as phlebitis, headache, sweating, or distress of any kind. A decided diuresis is noted in each case. After 2 hours diuresis sets in and within 20 hours as much as 2100 to 3500 cc. are excreted.

Our interest was particularly focussed upon the 7 cases of malignant hypertension and the 4 cases of chronic glomerular nephritis. In 10 of these the spinal fluid pressure ranged from 200 to 350 mm. of water. Diastolic blood pressure persisted above 130 mm. Hg. and choked disks were present



GRAPH 1.—The effect of intravenous sucrose on spinal fluid pressure and blood pressure in malignant hypertension.

in all except one case. Within 3 hours following the injection, spinal fluid pressure was reduced to a level of 40 mm. of water. Within from 3 to 24 hours, a gradual rise to basic level occurred.

In every case there was a prompt diuresis within 2 hours, although this was less pronounced in the nephritics than in the others. Headache, restlessness, nausea and vomiting were relieved. In no case was there a pronounced deviation of blood pressure from the original level. In no case were there any unfavorable effects of the treatment and the clinical condition of the patient seemed to be improved.

Comment. Patients with nephritis and those with hypertension of the malignant form frequently have signs and symptoms of increased intracranial pressure. The most distressing symptoms in this period are closely related to and probably caused by the increase of intracranial pressure. Uremic convulsions are associated with a very high diastolic blood pressure and an increased intracranial pressure. In the management of such cases it is desirable to reduce the spinal fluid pressure, in order to forestall convulsions and relieve symptoms and to promote diuresis for prevention of genuine uremic coma. From the experimental and clinical experiences of other workers, it is evident that a substance is desirable which will accomplish these results when given intravenously. To be of clinical value such a solution should have the following properties: 1, it

must be non-toxic when given in large doses of high concentration; 2, it must reduce spinal fluid pressure, sustain the low pressure for hours or days and must not cause a secondary rise above the basic level; 3, it should produce a prompt diuresis for the elimination of fluid is necessary for the reduction of spinal fluid and also for the prevention of retention of nitrogen products. According to the investigative work of Bullock, Gregersen, and Kinney⁴ and of Masserman,¹⁷ sucrose fulfills these conditions. It must be kept in mind that unless caution is used the intravenous injection of any hypertonic solution may be followed by unfavorable reactions. In cases of hypertension the heart may become embarrassed by the sudden increase of fluid in the vascular system. It may be noted that in our work we have used doses as large as 300 to 500 cc. of 50% solution intravenously without untoward effects. We believe it must be given slowly and the injection stopped at the first sign of disagreeable effects. To emphasize the non-toxic effects of sucrose, Bullock received 3 gm. per kg. body weight (432 cc. 50% solution) intravenously in 2 hours. There was no symptom except thirst, which was relieved on drinking water.

The effects of this therapeutic measure in our clinical work conforms fairly closely with those obtained by the above-mentioned research students. The prompt reduction of spinal fluid pressure without a subsequent secondary rise above the basic level, the relief from grave symptoms as headache, vomiting and vertigo, the prompt diuresis and the freedom from toxic reactions were features that encouraged us to apply this method in our work and to report the results. One of the chief recommendations of sucrose solution is that on repeated injections, no unfavorable results were noted in any case.

Summary. 1. A study is reported of the cerebrospinal fluid pressure and blood pressure of 21 cases of chronic hypertension.

2. There is not an exact correspondence between an elevation of cerebrospinal fluid pressure, papilledema and an excessively high diastolic blood pressure, but there is a close association between the three in most cases.

3. The effects of administering a 50% solution of sucrose intravenously are given. When 300 to 500 cc. of the solution are injected there is a prompt and prolonged reduction of spinal fluid pressure followed by a gradual return to the basic level in from 8 to 12 hours.

4. A prompt and profuse diuresis follows the injection; it begins about 2 hours after the injection and continues usually for 6 hours.

5. In this series of cases no unfavorable results were noted following the use of sucrose solution. Clinically, the patients were improved.

6. Intravenous injection of hypertonic (50%) sucrose solution is effective in reducing the elevated spinal fluid pressure that occurs in advanced arterial hypertension; diuresis is established and the aggravating symptoms such as headache, vomiting, vertigo, twitching, and dizziness, have been relieved.

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A CASE OF CEREBRAL DEGENERATION WITH ENCEPHALOGRAPHIC STUDY EIGHT YEARS AFTER COMMON CAROTID LIGATION.*

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SINCE Benjamin Travers first ligated the common carotid artery for the treatment of pulsating exophthalmos, this condition and its treatment have continued to interest the medical profession. Dandy, Matas, Kolodny, deSchweinitz and Holloway, Fuchs and others have studied the various therapeutic measures aimed at curing this condition.

* Presented at the New York Academy of Medicine, Meeting of the New York Neurological Society, December 3, 1935.

The following case is of interest because it demonstrates in a graphic manner the brain damage which may result from ligation of the common carotid artery.

Case Abstract. N. Q., a trained nurse, aged 57, entered this hospital on July 27, 1935, in a disturbed state. She was confused, disoriented as to time and place, showed gross defects of memory and intellect, and, in general, her condition was such as to make adequate contact impossible. She was quieted with sedatives, and the following history (for which I am in great part indebted to Dr. De Wayne Hallett) was obtained.

On November 1, 1926, the patient had been in an automobile accident. She bumped her head against the windshield but the only obvious injury was a laceration over the left eye. There was no loss of consciousness and the patient was able to return to work. Twelve days later her left eye became discolored and it began to protrude slightly. One month after the accident, she began to complain of noises in her head; she said they were like the swish of waves on the shore. Meanwhile the patient became more and more irritable, saying that the noise in her head was driving her mad. Roentgen films of the skull were reported as normal. She visited various specialists, none of whom was able to determine the cause of the patient's complaints. Seen for the first time by Dr. De Wayne Hallett 63 days after the accident, the condition was recognized as one of pulsating exophthalmos—probably due to a traumatic carotid-cavernous sinus aneurysm. The following characteristic triad was noted: (1) The left eye could definitely be felt to pulsate when the slightest pressure was put on the eyeball. (2) There was measurable exophthalmos of the left eye. (3) There was a subjective and an objective bruit. The latter could be heard all over the left side of the head. It was also noticed that the bruit stopped when the left internal carotid artery was compressed.

The patient was put to bed and 27 days later (90 days after the accident) under ether anesthesia the left common carotid artery was ligated by Dr. G. W. Roberts. The immediate effects were a complete cessation of the bruit, a right hemiplegia and total aphasia. Sensation was apparently not tested at that time.

The bruit recurred 14 days later in a light blowing form audible only at the outer angle of the left orbit. It ceased on carotid compression. On the 133d postaccident day, the left superior ophthalmic vein was ligated. Following this second operation the bruit stopped but the patient progressively lost vision in the left eye, so that by September, 1927, she could only perceive light in that eye.

Her neurologic examination at the time of her Bellevue Hospital admission revealed the following: There was about 3 mm. of exophthalmos in the left eye. The left pupil was larger than the right and reacted very poorly to light on direct stimulation—its consensual reaction was good. The left nerve head was pure white; the arterioles were very thin and the veins appeared collapsed as compared to the right eye. Her visual acuity was 16/20 in the right eye; she could only perceive light with the left eye. The visual field of the right eye was well within normal limits. She had a right hemiparesis, including the lower face with associated muscular atrophy. Her gait was typically hemiplegic. There was a downward drift of the outstretched right hand which was markedly accentuated when she closed her eyes. The deep reflexes were hyperactive on the right side and the right abdominal exhausted quickly. There was a right Hoffman sign but no Babinski. Sensory examination revealed a hypesthesia and hypalgesia to all forms of sensation—most marked peripherally in a glove and stocking fashion. She had completely lost position sense on the right side. Her right hand was asteriognostic. Both extremities on the right side showed

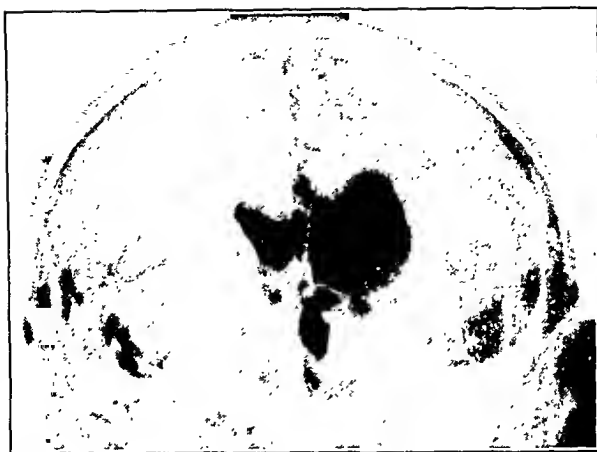


FIG. 1.—Anteroposterior view: Showing the marked dilatation of the anterior horn of the left lateral ventricle with an increase in the markings over the surface of the left cortex.



FIG. 2.—Postero-anterior view: Showing the dilatation of the posterior horn of the left lateral ventricle.

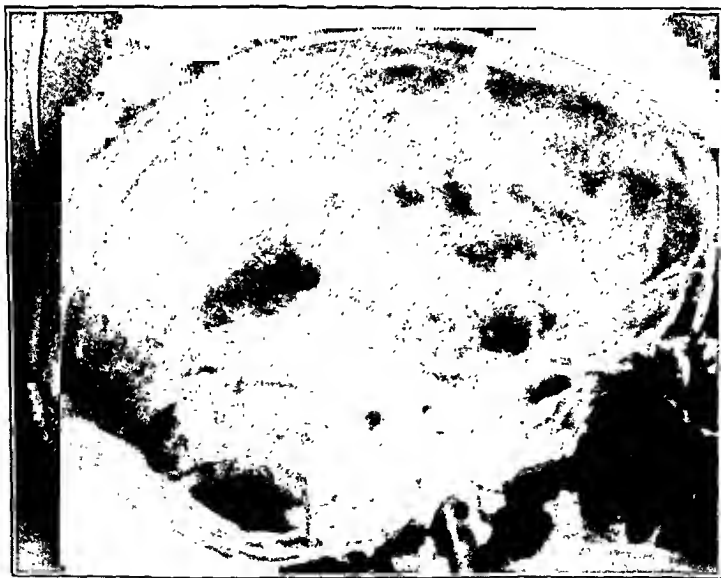


FIG. 3.—Right lateral view: Showing the dilated left lateral ventricle.

trophic edematous changes, most marked peripherally. She understood perfectly the spoken and written word. Her speech was slow and when she became tired or confused she developed a typical anomia which was not present at any other time.

No bruit could be heard anywhere over the head.

Her psychiatric survey is of interest. The patient has shown marked intellectual impairment since operation. She is no longer able to carry on her duties as a housewife and is almost completely dependent on her children. She has been picked up on street cars, wandering aimlessly about and completely amnesic. Her attitude toward her children has changed. She has become very demanding and irritable. Her daughter states that the patient has attempted suicide on two occasions—"never with any serious intent, but merely to attract attention to herself." Her mood during her hospital stay varied from that of a very coöperative and appreciative patient, to fits of choleric temper controllable only by large doses of sedatives.

Laboratory Data. (Bellevue Hospital, August 15, 1935.) Her blood pressure was 135/90 on both arms. Roentgen rays of the skull were normal. Six-foot heart plate revealed slight dilatation of the left ventricle. The encephalograms were of interest in that they revealed the typical unilateral "hydrocephalus *ex-vacuo*" characteristic of degeneration of one cerebral hemisphere. The red blood count was 4,900,000; hemoglobin, 90%; leukocytes, 7800 (normal differential count). N.P.N., 31; sugar, 87; calcium, 10.1; phosphorus, 4. Her spinal fluid contents were normal; initial pressure, 100.

Summary. 1. This record represents an 8-year follow-up of the neurologic and mental changes following ligation of the common carotid artery for pulsating exophthalmos (traumatic carotid-cavernous sinus aneurysm).

2. The encephalographic study illustrates the degree of brain damage which may follow ligation of the common carotid artery.

3. This case demonstrates the danger of completely ligating the common carotid artery without first encouraging the development of collateral circulation by digital compression.

I am indebted to Dr. Foster Kennedy, Director of the Neurological Service at Bellevue Hospital, for permission to report this case.

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THE EFFECT OF THE INJECTION OF CERTAIN NITROGEN-
CONTAINING COMPOUNDS INTO THE CISTERNA MAGNA
ON THE BLOOD PRESSURE OF DOGS.

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At one time or another most of the urinary protein derivatives have been indicted as responsible for the uremic syndrome. The voluminous literature on this subject has been summarized by Fishberg,¹ who has pointed out that there is no convincing evidence to support the idea of the importance of any of these substances in the production of the increase in blood pressure, or of the other clinical phenomena which may accompany renal insufficiency. Attempts to produce in animals a syndrome resembling uremia by administering these compounds orally and intravenously have resulted in failure. However, we do not believe that such negative results can be regarded as conclusive, in view of the fact that we have recently observed in acute experiments, increase in blood pressure, muscular twitchings, and stertorous breathing following the intracisternal administration of certain electrolytes.² These effects were obtained from doses which were entirely ineffective when given intravenously. For these reasons it was decided to investigate the central action of the nitrogenous "retention" products by injecting them into the cisterna magna of dogs.

The effects of urea, uric acid, creatinin, ammonia, amino-acids and guanidin have been observed. The technique employed has been described in the previous communication.² The animals were anesthetized with sodium pentobarbital. The volume of fluid injected intracisternally was in each instance 1 cc.

Results. *Urea.* The intracisternal injection of solutions of various strengths up to one-half molar did not cause significant change in blood pressure.

Sodium Urate. Saturated aqueous solutions containing approximately 6 millimols per liter (m. mols. p. L.) were ineffective. Inconstant effects were obtained with suspensions. In some instances suspensions containing 50 m. mols. p. L. were without effect; in other observations pronounced pressor responses occurred from the same dose.

Creatinin. Solutions containing 250 and (500 m. mols. p. L.) were ineffective in 4 or 5 observations. The pressor response obtained in the fifth instance was apparently due to osmotic alterations as a rise in blood pressure was produced by the injection of equimolar amounts of sodium chlorid.

Ammonia. Constant results were not obtained from the intracisternal injection of ammonium chlorid. In the majority of instances this salt was without effect but in several animals pronounced and well sustained increase in blood pressure occurred (Fig. 1a). The cause of the variability of the response is unknown.

In several instances ammonium salts were given intravenously, the lactate being substituted for chlorid in order to avoid acidosis. Repeated injections of this salt caused temporary decline in blood pressure followed by a more sustained rise (Fig. 1b). However, pressor responses were not obtained until amounts approaching the lethal dose had been given.

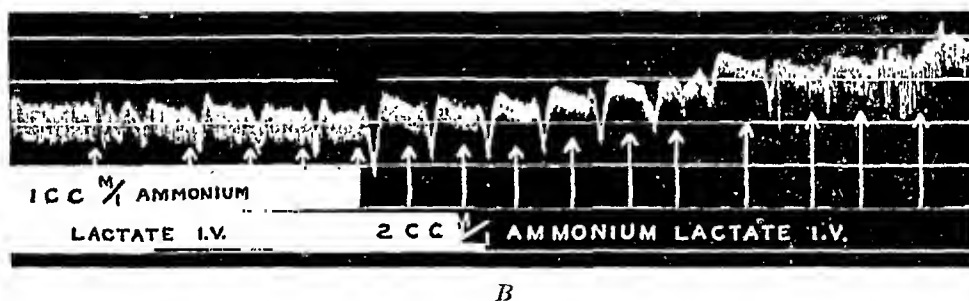
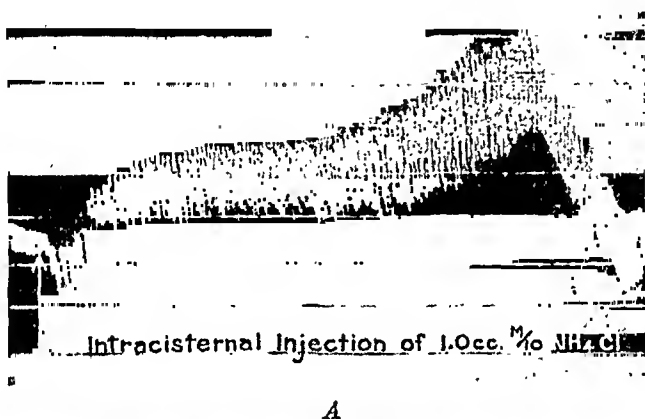


FIG. 1.—The curve in this and other figures passes from left to right, and the distance between two adjacent horizontal lines indicates 20 mm. of mercury. The time curve in the lower portion of the record designates 6-second intervals. A. Intracisternal ammonium chlorid caused a marked rise in blood pressure. B. The effect of repeated intravenous injections of ammonium lactate is shown. Shortly after the last injection the animal died of respiratory paralysis.

Amino-acids. The concentrations employed of the several compounds varied according to their solubilities. Negative results were found with saturated solutions of cystin, cystein hydrochlorid, and tyrosin. Consistent pressor effects were not observed after intracisternal injections of d-arginin (100 m.mols p. L.), histidin dichlorid (50 m.mols p. L.), glycine (100 m.mols p. L.), leucin (100 m.mols p. L.), phenyl alanin (100 m.mols p. L.) or d-l alanin (50 m.mols p. L.). Striking rise in blood pressure occurred after injection of lysin picrate but the response could not be ascribed to the

ICC M/30 ASPARTIC ACID INTRACISTERNALLY

B ICC M/40 GLUTAMIC ACID INTRACISTERNALLY

ICC M/20 GLUTAMIC ACID INTRACISTERNALLY

ICC M/20 Na₂HPO₄ INTRACISTERNALLY

ICC M/20 GLUTAMIC ACID INTRACISTERNALLY

ICC M/20 Na₂HPO₄ INTRACISTERNALLY

ICC M/20 GLUTAMIC ACID INTRACISTERNALLY

ICC M/20 Na₂HPO₄ INTRACISTERNALLY

ICC M/20 GLUTAMIC ACID INTRACISTERNALLY

FIG. 2.—The two upper curves (A and B) illustrate the pressure responses to the intracisternal administration of aspartic acid and glutamic acid. The three lower curves were obtained from a different animal, which was at first unresponsive to glutamic acid (C). Following the intracisternal administration of phosphate the same amino acid caused a rise in blood pressure (D and E).

ICC M/ GUANIDINE HYDROCHLORIDE INTRAVENOUSLY

ICC M/ GUANIDINE HYDROCHLORIDE INTRACISTERNALLY

FIG. 3.—The upper curve shows the absence of response to guanidin hydrochlorid administered intravenously, the same dose being effective when given intracisternally as shown in the lower curve.

lysin for picric acid gave similar results. Aspartic acid (30 m.mols p. L.) and glutamic acid (50 m.mols p. L.) gave inconstant effects. When positive results were obtained with these two amino-acids the pressor responses usually lasted for 15 minutes or longer (Fig. 2) and were more persistent although less marked than those obtained

from some of the electrolytes investigated in our previous study.² It was found that the injection of calcium salts would lower the blood pressure which had been increased by glutamic acid. Diminution in the spinal fluid calcium by injecting di-sodium phosphate appeared to increase the pressor effect of glutamic acid (Figs. 2c, 2d, and 2e). However, calcium salts did not prevent the pressor response from a subsequent injection of glutamic acid.

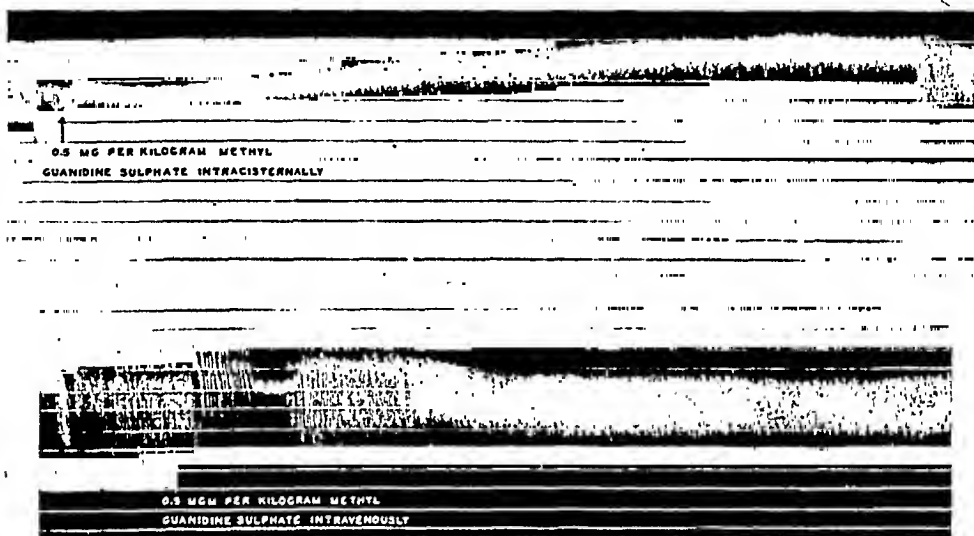


FIG. 4.—The time curve in the lower portion of the record designates 6-second intervals. Methyl guanidin sulphate intraeisternally caused a slowly developing but sustained rise in blood pressure with an increase in respiratory fluctuation. The same dose was ineffective when later administered intravenously to the same animal.

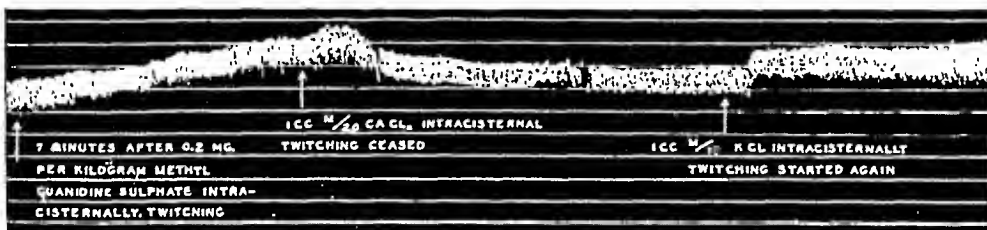


FIG. 5.—The time curve in the lower portion of the record designates 6-second intervals. At the onset of the record the blood pressure was rising and the animal had developed twittings following the previous administration of methyl guanidin. Calcium chlorid caused a cessation of muscular twittings and a fall in blood pressure, these effects being reversed by potassium chlorid. [Ordinarily, intracisternal injection of potassium salts is ineffective for several hours following the administration of calcium salts.² The record shows that the previous administration of guanidin interferes with the inhibitory action of calcium salts.]

Guanidin. Intracisternal injection of guanidin hydrochlorid caused rise in blood pressure when the same dose was ineffective intravenously (Fig. 3). Similar results were obtained with methyl guanidin sulphate (Fig. 4), which proved effective in smaller dosage than the guanidin itself. Intracisternal injections of as little as 0.2 mg. per kg. of methyl guanidin sulphate caused pronounced rise in blood pressure (Fig. 5).

The pressure effects of the guanidin compounds were slow in onset and often persisted for an hour or more. Marked respiratory stimulation and muscular twitchings usually accompanied the rise in blood pressure. Calcium salts administered intracisternally controlled the twitchings and diminished the blood pressure, regardless of whether the guanidin had been given intravenously or intracisternally (Figs. 5 and 6). Similar doses of calcium salts administered intravenously were less effective (Fig. 6).

The pressor effect of potassium chlorid when administered intracisternally can ordinarily be prevented by the previous injection of calcium salts.² However, when guanidin was given first the calcium was no longer effective in this respect (Fig. 5).

In a series of experiments Mason and Resnik³ have shown that the lethal dose of calcium salts administered intracisternally to dogs

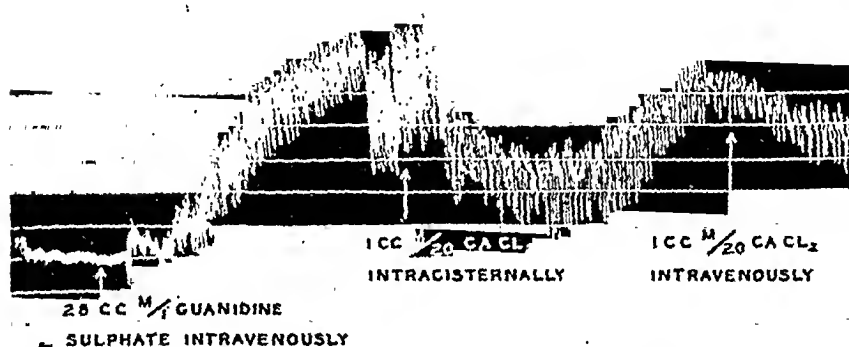


FIG. 6.—The time curve in the lower portion of the record designates 6-second intervals. Following a large intravenous dose of guanidin there was a marked increase in the blood pressure. Intracisternal administration of calcium chlorid produced a marked but temporary decline. The same dose of calcium chlorid administered intravenously had a less striking effect.

is in the general region of 0.3 to 0.4 mg. of calcium per kg. of body weight. In the present observations it was found that animals which had received guanidin either intravenously or intracisternally were able to tolerate larger doses of calcium chlorid.

Discussion. Of the several compounds investigated consistent and striking pressor effects were obtained only with guanidin and its methyl derivatives. Inconstant results were encountered with sodium urate, ammonia, aspartic acid and glutamic acid. As regards uric acid the positive results cannot be regarded as of significance because they were inconstant and were obtained only with suspensions, which may possibly have produced some mechanical irritation. Although ammonium salts caused pronounced rise in blood pressure in some experiments there is no reason to believe that they can be concerned in the elevation of blood pressure in patients with renal insufficiency, for the concentration of ammonia

in the body fluids never approaches the amounts necessary to cause increase in blood pressure in the animals. The same may be said of glutamic acid and aspartic acid although the possibility remains that under certain conditions the concentration of amino-acids in the cells of the nervous system may be greater than that in the body fluids.

It has been clearly shown by other investigators that guanidin has a peripheral pressor effect. [The literature on this subject has been summarized by Goldblatt and Karsner⁴.] On the other hand, in our experiments the pressor effects of guanidin and of methyl guanidin were more pronounced when these substances were given intracisternally than when they were administered intravenously in equal dosage. Furthermore, the effects of guanidin were neutralized by the intracisternal administration of calcium salts in doses which were less effective intravenously. These observations indicate that under the conditions of our experiments the action of guanidin was chiefly central rather than peripheral.

The muscular twitchings, stertorous breathing and increase in blood pressure observed in the dogs which received guanidin constituted a symptom complex which was rather similar to that observed in many patients with advanced renal insufficiency. Whether or not this substance is concerned in the pathogenesis of the uremic symptom complex must be decided by future work. In such investigations the central as well as the peripheral action of guanidin must be taken into account.

Summary. The intracisternal injection of urea and creatinin did not increase the blood pressure. Uric acid (as sodium urate) and ammonia produced inconstant results. Of the several amino acids studied positive results were obtained only with aspartic acid and glutamic acid.

Guanidin hydrochlorid and methyl guanidin sulphate, when injected into the cisterna magna, caused striking and prolonged rise in blood pressure and muscular twitchings. Similar doses administered intravenously were less effective. Intracisternal injection of calcium salts diminished the blood pressure and controlled the muscular twitchings previously induced by guanidin. The observations indicate that guanidin has, in addition to the peripheral effect which has been described by others, a pronounced action on the central nervous system.

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BLOOD PHOSPHATASE AS AN AID IN THE DIFFERENTIAL DIAGNOSIS OF JAUNDICE.

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PHOSPHATASE is the term applied to one or more enzymes normally present in most tissues of the body and apparently concerned in the metabolism of bone. It is found in relatively large concentrations in bone, liver, kidney, and intestinal mucosa. It is also present in blood, bile and feces, and occasionally in traces in the urine.

Robison,¹ the first to demonstrate the presence of this enzyme in bone and ossifying cartilage, showed its intimate relationship to the process of bone formation. Since then it has been studied in the blood and its quantitative estimation in blood serum and plasma has been of considerable diagnostic value in a limited group of pathologic conditions, particularly diseases of bone.²⁻⁵ The serum and plasma phosphatase have been reported to be moderately increased in cases of pronounced local bone atrophy, generalized osteoporosis and osteomalacia. In the few reported cases of hyperparathyroidism the findings are 4 and 5 times the normal. Active infantile rickets are found to be associated with very high phosphatase readings, reaching on occasions values from 10 to 13 times the normal figures. The greatest elevations have been found in florid polyostotic Paget's disease, in which condition values as high as 30 times the normal have been reported. In osteogenic sarcoma, metastases to bone and fragilitas ossium the phosphatase value is said to be moderately increased. Physiologically, the phosphatase content of the blood plasma is slightly increased after the ingestion of carbohydrates.⁶

Roberts,⁷ who was among the first systematically to study the blood phosphatase in disease states, observed high values in the 3 cases of jaundice which he had included in his series. He noted, moreover, a striking difference in the phosphatase content of the plasma of the 2 cases of obstructive and the 1 case of non-obstructive jaundice studied. This observation led him, in a subsequent work,⁸ to study the phosphatase values in a series of 52 cases of jaundice, 21 of which were obstructive, 31 non-obstructive. He concluded that by means of the phosphatase level of the blood, "toxic, infectious and catarrhal jaundice may be readily distinguished from jaundice of the obstructive type." In this series he found, as others

have also, normal phosphatase values in 5 cases of hemolytic jaundice. Subsequent workers, Bodansky and Jaffe,⁹ Armstrong, King and Harris,¹⁰ Greene, Shattuck and Kaplowitz,¹¹ also observed a rise of phosphatase value in all cases of jaundice other than that of hemolytic origin. Bodansky and Jaffe¹² ligated the common bile duct of a dog and noted the progressive elevation in the serum phosphatase paralleling the rise in the serum bilirubin. They believed, however, that the determination of plasma phosphatase was of no value in differentiating between obstructive and non-obstructive jaundice.

Armstrong, King and Harris¹⁰ confirmed these ligation experiments in 19 dogs and, after releasing the obstruction in 2 animals, noted a return to normal in the phosphatase and bilirubin values. In 1 the drop in the plasma phosphatase was immediate, in the other the return to a normal phosphatase value was more gradual. They believed that this slow return to normal was the result of damage to the liver cells incurred during the period of biliary obstruction. They also report phosphatase studies in 5 clinical cases of obstructive jaundice, obtaining results comparable to those in the experimental animals whose common bile ducts were ligated. Armstrong and King¹³ later produced a toxic hepatitis in 8 dogs (chloroform, phosphorus and toluyldiamin) with a resulting elevation in the phosphatase values. In 2 other dogs a marked phenylhydrazin hemolysis, in accord with results of other workers, produced no elevation of phosphatase. The elevation of phosphatase which developed in the 8 animals with toxic hepatitis, however, at no time reached the levels obtained in the cases of experimental obstructive jaundice, even in the instances of the most severe liver damage. They concluded from these experimental studies that the test may, with further investigation, become useful in the differential diagnosis of jaundice. Greene, Shattuck and Kaplowitz,¹¹ on the other hand, concluded from a series of clinical cases that the test was of no value in differentiating between obstructive and non-obstructive jaundice.

It is the purpose of this paper to present clinical data which we believe substantiate Roberts' original assertion concerning the clinical usefulness of phosphatase determinations in the differential diagnosis of jaundice.

It is unnecessary to point out the importance of determining the mechanism of the production of jaundice in particular cases, and the desirability of arriving at some notion of the pathologic state of the liver under such conditions. Soffer,¹⁴ in a recent review of liver function tests, has again emphasized the profound inadequacies in the present state of our knowledge. Though nearly all the liver function tests suggested at various times have contributed information of value and, in some instances, have been of aid in differential diagnosis, it is generally agreed, by most authorities, that individually and collectively they fall far short of our needs. We feel that the addition of the results of the phosphatase test contributes information of definite value.

The classification of jaundice under which we have arranged our cases is the following orthodox grouping into:

1. Obstructive jaundice, *i. e.*, jaundice due to extrahepatic obstruction including cases of obstruction due to stones in the common bile duct, neoplasm, etc.

2. Hepato-cellular or non-obstructive jaundice, *i. e.*, jaundice resulting from direct injury to the parenchymal liver cell, or to cholangitis, such as is the case in so-called "acute catarrhal jaundice."

3. Hemolytic jaundice.

Methods. At present several methods are used to determine the phosphatase activity of the blood.^{7,15,16,17} They are essentially similar in principle. They consist in measuring the phosphorus set free as inorganic phosphate when the enzyme present in the blood is allowed to act on a phosphoric acid ester substrate under standardized conditions. Some methods employ blood serum, others plasma; each varies in the nature of the buffer, and time of incubation, and some in the methods employed in determining the inorganic phosphorus content of the blood. Unfortunately there is at present no general agreement among workers in reporting the results of phosphatase determinations. The units of measurement in the various methods vary. We have employed a slight modification of Roberts'¹⁷ method in our present study which is practical, simple, time saving and entirely satisfactory for clinical purposes. The method is as follows: The determinations are made on fasting blood. Two cc. of plasma (citrate blood) is mixed with 2.3 cc. of distilled water and 0.7 cc. of N/10 sodium hydroxid. This produces a pH of approximately 8.9. To this is added 1 cc. of a 1% solution of sodium beta-glycerophosphate. The mixture is then incubated at 37.5° C. for 2 hours, after which its inorganic phosphorus content is determined by the method of Fiske and Subbarow. At the same time the initial inorganic phosphorus content of the plasma is determined using another 2 cc. of the original blood. Both of these values are determined in mgm. per 100 cc. of blood plasma. The difference between these two values represents the number of mgm. of inorganic phosphorus liberated by the enzyme, phosphatase, from the substrate under the above conditions. Each mgm. thus obtained is expressed as units of phosphatase per 100 cc. of blood plasma.

In addition to the determination of the phosphatase in cases of jaundice, during the past 3 years, we have also studied the values on a series of cases exhibiting no jaundice and without, as far as we were able to determine, any appreciable liver damage, or any of the other pathologic states known to influence phosphatase values. These include 18 cases of cholecystitis with and without stones. Table 1 lists the values in these cases.

TABLE 1.—PHOSPHATASE VALUES IN CASES WITHOUT JAUNDICE OR LIVER DISEASE.

No. of cases.	Age range, years.	Units of phosphatase.
10	1 to 15	3.20 to 10.80
5	16 to 20	1.70 to 5.80
14	21 to 30	2.00 to 6.00
19	31 to 40	1.00 to 5.90
9	41 to 50	2.30 to 4.40
10	51 to 60	1.60 to 6.00
5	61 to 70	2.30 to 4.90
2	71 to 80	1.80 to 3.00

Taking into consideration the results listed in Table 1 and those given by Roberts,⁷ we have regarded as normal for adults, phosphatase values less than 6 units, and for children values less than 15 units.

TABLE 2.—CASES OF OBSTRUCTIVE JAUNDICE.

No.	Name.	Age.	Date.	Units of phosphatase.	Serum bilirubin, mgm.	Remarks and diagnoses.
1	R. G.	20	9/14	20.48	5.28	Galactose excretion in 5 hours
			9/17	22.02	4.28	was 2.9 gm.
			9/18	11.08	2.47	Operation 9/20—stone in common duet.
			9/18	12.64	3.92	
			9/20	14.98	5.78	Expired 9/23. No necropsy.
2	S. H.	52	1/22	23.40	5.09	Roentgen ray showed gall stones.
			1/27	15.54	Not done	
3	L. M.	19	12/28	20.58	2.12	Operation on 1/26 revealed gall stones.
			1/2	19.50	0.50	
			1/11	14.04	0.78	
			1/30	6.70	0.54	
4	S. R.	60	12/26	18.82	5.42	Diabetes mellitus. Operation on 1/4—stone removed; gall bladder gangrenous. Elevation of phosphatase on 1/19 suggests partial obstruction. Patient drained bile until discharge.
			1/2	18.06	6.23	
			1/11	5.40	5.08	
			1/16	9.22	3.08	
			1/19	23.92	4.06	
			1/25	15.08	3.90	
			2/1	24.42	1.48	
			2/13	23.18	1.42	
5	A. O.	65	2/20	20.08	1.32	
			11/11	19.04	1.56	Roentgen ray showed gall stones.
6	L. S. Readmission	65	12/7	10.18	1.24	On 11/28, icterus index 72. On 11/29 stones found in common bile duet. Readmitted. Expired on 3/1. Necropsy: sub-diaphragmatic abscess and acute hepatitis.
			2/24	1.36	8.25	
			2/26	7.00	11.31	
7	H. S.	52	6/7	19.00	0.75	Biliary drainage revealed crystals and pigment. Diagnosis of gall stones.
			6/8	15.40	0.45	
			6/13	10.30	0.37	
8	J. D.	53	7/13	21.48	1.55	
			7/18	17.26	1.53	
9	R. P.	70	4/12	18.32	2.58	Operation on 4/12, and stones were found in the common bile duet.
			4/16	13.12	0.96	
			4/21	7.00	0.31	
10	J. H.	35	3/15	14.14	0.62	Biliary drainage showed calcium bilirubinate pigment and cholesterol crystals.
			3/17	14.30	0.58	
			3/19	17.98	1.65	Operation on 3/22: showed gall stones.
			3/21	11.18	Not done	
11	S. F.	60	3/24	6.92	0.86	
			6/12	12.24	2.26	Operation on 6/13: common bile duet filled with stones.
12	G. Y.	52	11/9	11.36	0.58	Biliary drainage; pigment and crystals.
13	A. K.	46	7/30	7.46	0.90	Operation, 7/31: gall stones.
			8/2	6.10	0.81	
			8/8	4.18	0.35	
14	B. W.	42	2/1	10.56	1.85	Operation, 2/15: gall stones and a dilated common bile duet.
			2/6	13.04	0.52	
			2/20	10.58	0.92	
15	J. B.	40	11/17	14.44	9.24	Block in sphincter of Oddi by plug of mucus and duodenitis.

TABLE 2.—CASES OF OBSTRUCTIVE JAUNDICE—Continued.

No.	Name.	Age.	Date.	Units of phosphatase.	Serum bilirubin, mgm.	Remarks and diagnoses.
16	J. P.	60	8/22 8/25	20.96 17.66	1.81 2.00	On 2/13, 6 months before present admission, had gall bladder operation, now postoperative adhesions.
17	T. W.	53	11/2	12.44	7.29	Two previous operations. Now periductal adhesions.
18	C. H.	26	12/19 12/21 12/28 1/6	3.00 4.50 4.62 2.94	1.01 0.58 0.70 0.45	Operation, 1/9: stone in the cystic duct.
19	M. M.	46	3/23 3/27 3/30 4/3 4/12 4/19	20.76 19.32 21.40 19.80 21.64 12.70	Not done " " " " "	Icterus index on these successive dates were 16; 22.4; 47.6; 14.8; 6.2 and 5.1. The serology was positive. Operation, 4/5: dilated common bile duct due to stones.
20	N. W.	38	12/19 12/22 1/11	6.04 6.80 4.86	1.42 1.65 0.46	Operation, 12/23: gall stones and acute pancreatitis.
21	S. M.	31	5/29 5/31 6/2 6/5	10.80 13.18 13.78 5.22	1.09 0.74 1.35 0.42	Gall stones with chronic hypertrophic biliary cirrhosis. Urobilinogen were 1 to 200 and 1 to 400.
22	F. P.	27	3/8 3/10 3/13 3/19 3/21	8.18 7.44 4.84 3.84 3.48	3.99 3.90 1.52 0.64 Not done	Biliary drainage showed pigment and crystals. Operation, 3/22: gall stones with adhesions.
23	D. W.	57	1/13 1/20 2/8 2/12	22.68 20.78 14.56 20.80	1.08 3.11 2.63 Not done	Necropsy, 2/15: carcinoma of head of pancreas with metastases to liver.
24	A. K.	70	11/11 11/23	10.60 11.00	7.34 9.23	Necropsy, 11/24: carcinoma of head of pancreas. Galactose excretion in 5 hours was 3 gm.
25	S. B.	65	4/24 4/26 4/28 5/2 5/5 5/8	25.04 25.56 21.80 24.64 20.16 23.72	9.50 8.97 10.58 9.79 7.84 7.44	Necropsy, 5/15: carcinoma of head of pancreas. Galactose excretion in 5 hours was 3 gm.
26	S. W.	62	5/5 5/10 5/16 5/19	23.90 24.78 11.94 Not done	6.48 7.98 4.74 4.76	Cholecystostomy, 5/12. Necropsy, 5/28: carcinoma of head of pancreas.
27	M. C.	60	9/14 9/17 9/20 9/22	21.60 22.08 19.58 21.62	8.70 7.56 12.62 12.91	Necropsy, 9/26: carcinoma of head of pancreas with liver metastases.
28	S. F.	70	7/26 8/4	20.20 17.56	6.67 6.60	Necropsy, 8/4: carcinoma of head of pancreas.
29	Y. G.	62	10/11 10/21 12/21	19.04 10.60 18.60	16.56 10.89 16.23	Diabetes mellitus with carcinoma of head of pancreas.

Our series consists of 53 cases of jaundice of various mechanisms, and are listed in Tables 2 and 3. The phosphatase determinations were repeated at frequent intervals in many instances. Quantita-

tive serum bilirubin determinations were done simultaneously in most instances. Only those cases in which the diagnosis was well established by clinical and laboratory findings were included in this study.

In Table 2 are listed the results of a series of 29 cases of obstructive jaundice. Several etiologic factors were involved as can be seen from this table. The generally high phosphatase values are striking. In all but 4 of the 29 cases the phosphatase values were greater than 10 units. These findings are in marked contrast with those obtained in the series of non-obstructive cases listed in Table 3. In Case 1, the medical and surgical consultants disagreed as to the diagnosis, the latter inclining to a diagnosis of toxic hepatitis refused to operate. On September 20, following a severe chill, the patient was operated upon and a stone was found impacted in the common bile duct. In Case 6, the phosphatase reading of 10.18 units was obtained during the period of convalescence, following a cholecystectomy for common duct obstruction. When the patient was readmitted a medical diagnosis of recurring common duct obstruction was made. The phosphatase values obtained at this time, 1.36 and 7.00 units, suggested rather a jaundice resulting from a non-obstructive mechanism. An acute hepatitis was found at necropsy.

In Table 3 are listed the findings in 24 cases of non-obstructive jaundice. In 18 of these the phosphatase values lie at or below 10 units. In 4 cases (Nos. 33, 39, 41 and 43) values slightly greater than 10 units were obtained. In the remaining 2 cases (Nos. 34 and 47) values as high as 17.26 and 11.68 units were obtained respectively. These last 2 were children in whom phosphatase values as high as 15 units are considered normal. It is therefore justifiable to regard the results obtained in Case 34 as moderately increased above normal, and that in Case 47 as falling within the normal range. It is because of these findings and those listed in Table 2 that we have come to agree with Roberts in his assertion that in cases of jaundice, phosphatase values up to 10 units indicate that the jaundice is non-obstructive in etiology, and values above 10 units indicate an obstructive mechanism.

Discussion. In commenting on the results in Table 3, we have called attention to a number of instances in which the phosphatase values were greater than 10 units. We cannot, however, entirely agree with Roberts⁸ when he states that it is not necessary to know the concomitant serum bilirubin values in order to interpret the phosphatase readings. We believe that a comparison of the relative increase in the values of phosphatase and serum bilirubin above their respective normals gives additional aid in diagnosis, and in particular makes possible a correct interpretation of those borderline values of 10 units or slightly above. The basis for this belief lies in the observation that in obstructive jaundice the rise in the phosphatase and serum bilirubin tends to run parallel until the limits of the phosphatase values are reached. In non-obstructive

TABLE 3.—CASES OF NON-OBSTRUCTIVE JAUNDICE.

No.	Name.	Age.	Date.	Units of phosphatase.	Serum bilirubin, mgm.	Diagnosis.	Remarks.
30	A. R.	30	6/13 6/18	6.30 7.30	8.90 4.60	Hepato-cellular jaundice	Urobilinogen 1:100. Galactose excretion 4 gm. in 5 hours.
31	F. V.	17	6/9 6/13 6/18	10.00 5.50 8.00	10.00 6.00 5.00	Hepato-cellular jaundice	Urobilinogen 1:100. Galactose excretion 4.7 gm. in 5 hours.
32	R. D.	24	3/16	5.84	2.30	Gall stones, hepatitis, cystic duct obstruction	Urobilinogen 1:100. Galactose excretion 2 and 4.78 gm. in 5 hours. Positive serology. Operation.
33	B. S.	37	5/25 5/28 6/9 6/13	10.50 7.92 9.00 9.00	12.18 8.19 2.40 1.84	Hepato-cellular jaundice	Urobilinogen 1:50. Galactose excretion 1.35, 3.08 and 5.55 gm. in 5 hours. Chronic alcoholic. Takata-Ara test positive.
34	N. W.	11	1/25 2/2 2/6	10.12 17.26 16.20	2.41 1.25 0.54	Hepato-cellular jaundice	Urobilinogen 1:40. Roentgen ray normal gall bladder, no stones.
35	W. H.	35	1/20 1/22 1/23	3.14 4.34 2.86	3.00 3.39 1.89	Hepato-cellular jaundice	Urobilinogen 1:20. Galactose excretion 0 gm. in 5 hours. Roentgen ray no gall stones.
36	C. F.	36	2/14 2/21	9.28 8.68	8.64 4.71	Hepato-cellular jaundice	Urobilinogen 1:80. Galactose excretion 0 gm. in 5 hours.
37	J. J.	38	8/17	8.04	5.00	Hepato-cellular jaundice	Urobilinogen 1:50. Galactose excretion 6.7 gm. in 5 hours.
38	R. C.	25	12/3	6.34	7.10	Hepato-cellular jaundice	Urobilinogen 1:20.
39	S. S.	26	1/9 1/19	11.38 7.24	12.40 5.90	Hepato-cellular jaundice	Urobilinogen 1:8. Galactose excretion 2.2 gm. in 5 hours.
40	A. I.	28	12/18	9.38	7.10	Hepato-cellular jaundice	Galactose excretion in 5 hours 0.83 gm.
41	T. P.	21	12/29 1/2 1/21	10.34 9.02 3.78	9.76 5.79 0.72	Hepato-cellular jaundice	Urobilinogen 1:20. Galactose excretion 4.79 gm. in 5 hours.
42	E. K.	7	11/10 11/12 11/20 12/5	9.52 10.04 9.04 7.04	7.76 6.67 5.78 2.20	Hepato-cellular jaundice	Urobilinogen 1:20.
43	N. K.	50	5/8 5/12	9.84 10.70	14.30 17.80	Acute yellow atrophy	Galactose tolerance test unsatisfactory.
44	J. P.	53	2/11	5.84	0.84	See Case 16	Admission prior to operation for cholecystitis.
45	D. G.	24	5/16 5/19 5/23 5/28 6/8	6.66 8.40 4.16 1.56 3.94	5.95 6.92 1.20 0.99 0.21	Hepato-cellular jaundice	Urobilinogen 1:100.
46	S. G.	6	3/1 3/10 3/21	8.82 8.98 4.46	3.77 1.94 0.67	Hepato-cellular jaundice	Urobilinogen 1:20.
47	E. K.	12	5/15	11.68	0.87	Hepato-cellular jaundice	Urobilinogen 1:20.
48	H. B.	43	7/21	4.55	0.70	Luetic hepatitis	Urobilinogen 1:90. Serology positive.
49	N. L.	53	11/25	2.58	3.43	Luetic hepatitis	Serology positive.
50	H. A.	63	1/25 2/1	1.92 3.00	1.54 0.60	Toxic hepatitis	Diabetes mellitus.
51	J. R.	66	7/13	4.32	0.76	Toxic hepatitis	Uremia.
52	D. W.	40	12/7 12/14	3.92 3.22	1.12 0.75	Pernicious anemia	
53	G. T.	48	5/25	8.32	1.64	Portal cirrhosis	Urobilinogen 1:100. Galactose excretion 1.36 gm. in 5 hours.

cases, on the other hand, in spite of the progressive increase in serum bilirubin the phosphatase values rarely rise above 10 units and no parallelism was noted. This is illustrated in the group of Cases 39, 40 and 41. Here we found phosphatase values ranging from 9.38 to 11.38 units, with serum bilirubin values of from 7.10 to 12.40 mgm. It is in such borderline cases that were the phosphatase alone considered it would be difficult to arrive at a definite interpretation. We would be forced, if we adhered too strictly to the value of 10 units, as the dividing line, to consider one of these (Case 39) as an instance of obstructive jaundice. In conjunction with the serum bilirubin estimation, however, the interpretation becomes clearer. The high phosphatase values usually associated with elevated bilirubin values in obstructive jaundice is absent. It would therefore seem justifiable to assert that the phosphatase values slightly greater than 10 units, if associated with a markedly elevated bilirubin justify the presumptive diagnosis of a predominantly non-obstructive mechanism. In the light of this qualification there need be in most instances no difficulty in the interpretation of borderline values.

We believe, therefore, from the striking differences in phosphatase values obtained in the two great groups of cases of jaundice discussed, that the blood phosphatase reflects two mechanisms, that due to obstruction and that due to a more direct involvement of the liver parenchyma. When both of these disturbances are present the extent of each can be roughly gauged by comparing the bilirubin with the phosphatase values. The phosphatase findings should, we feel, be considered as representing a composite of effects the dominant pathologic state exerting the greater influence on its value.

It is of course apparent from our data that the test can serve only as a means of differentiating between the two classes of jaundice we have listed, in the absence of other conditions affecting phosphatase. The specific etiology must, at the present time, be inferred from other studies. In its ability to help differentiate between an obstructive and an non-obstructive jaundice, however, the phosphatase determination appears to be superior to other available tests, and in particular, the galactose tolerance test, when the latter is used to detect acute parenchymal liver disease. Thus, the phosphatase findings were correct in most of the adult cases of non-obstructive jaundice, while in a considerable number of instances the galactose tolerance test was in error (Table 3). Only after repetition of the galactose tolerance test was the excretion, in some instances, elevated to levels diagnostic of hepato-cellular jaundice.

In our work we now regard the phosphatase values as a sensitive indicator of liver dysfunction in obstructive jaundice. In Case 7, the phosphatase value remained elevated long after the serum bilirubin and other findings had returned to normal. In this respect it appears comparable to the urobilinogen determinations in case of non-obstructive jaundice. One of us (M. M. R.)¹⁸ has shown

that urine urobilinogen will frequently remain increased in cases of hepato-cellular jaundice long after other tests have reached normal levels. It is also apparent from our studies that in some instances too much reliance must not be placed upon a single phosphatase determination. If, for example, a first estimation of phosphatase were to be made early in the onset of obstructive jaundice, as the jaundice is developing, it is conceivable that the phosphatase value, rising slowly in proportion, may not as yet have reached diagnostic heights. The low phosphatase value obtained under such conditions may be misleading. It is therefore necessary in some instances where the clinical impression of obstructive jaundice seems well founded, and the serum bilirubin only slightly elevated, to repeat both determinations within a few days in order to determine the progress of the disease. A similar caution must be exercised in the converse state. Furthermore, if the patient has had present a ball-valve stone or a biliary colic, due to the passage of stone too small to have produced more than a fleeting or latent jaundice, the phosphatase and serum bilirubin values may be only slightly increased. We have also noted a tendency, in insulin-treated diabetics with jaundice, for the phosphatase values to remain high postoperatively for a longer period of time than usual.

Summary. 1. The blood phosphatase values have been studied in a large series of clinical cases of jaundice, both obstructive and non-obstructive.

2. The phosphatase values in most of the cases of obstructive jaundice were found to have values greater than 10 units, while in the non-obstructive cases the values were found to be 10 units or less.

3. We, in agreement with Roberts, have therefore chosen a phosphatase value of 10 units to be the dividing line between cases of obstructive and non-obstructive jaundice. Certain considerations are listed which make more readily interpretable borderline cases.

4. The phosphatase determination has proven, in our studies, to be of greater value than any other available test in differentiating between obstructive and non-obstructive jaundice.

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COMPARATIVE ADVANTAGES AND FURTHER MODIFICATION OF THE BILIRUBIN EXCRETION TEST FOR HEPATIC FUNCTION.

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THE measurement of the excretion of intravenously injected bilirubin as a means of determining the existence of hepatic dysfunction was originally devised by Eilbot,¹ and was introduced into this country by Harrop and Barron.² The procedure, with the modifications to be described, appears to be the most delicate excretory test of liver function. It is hoped that the following data, and the improvements in the procedure resulting in the simplification of the test, will encourage its more widespread use.

The use of the bilirubin excretion test is limited to those patients who show no elevation of circulating blood bilirubin beyond 1 mg. %. In the presence of hyperbilirubinemia, the retention of injected bilirubin has no significance, since, obviously, the liver cannot adequately handle the amount of bile pigment in the blood prior to performance of the test.

In investigating the comparative merits of this method with bromsulphalein, levulose tolerance, galactose tolerance, urobilinogen and Van den Bergh procedures, it was found that the bilirubin excretion test yielded the greatest incidence of positive results.³ However, for closer evaluation, a comparison was made between bilirubin and bromsulphalein, both excretory gauges of hepatic function.

We have had no experience with rose bengal which is also used to determine the excretory capacity of the liver. We were influenced by Greene's observation⁴ that in a study of more than 700 cases "there is very little difference in the significance of the various dyes. Phenoltetrachlorophthalein, bromsulphalein and rose bengal all show essentially the same type of changes." Therefore, the bromsulphalein test has been used because it is the simplest to perform.

The relative merits of bromsulphalein and bilirubin are demonstrated in Table 1. In 18 cases in which there was clinically well-defined, although slight, liver damage, the bilirubin test was positive in 16, while in only 3 instances was functional derangement manifested by the bromsulphalein test. In 15 cases in which there were no clinical data to indicate hepatic involvement but where such a possibility was suspected (see Miscellaneous in Table 1), 17 com-

TABLE 1.—COMPARATIVE VALUE OF BILIRUBIN AND BROMSULPHALEIN LIVER FUNCTION TESTS.

Type of hepatic damage.	No. of cases.	Comparative tests.	No. of positive results.	
			Bilirubin tests.	Bromsulphthalein tests.*
Cirrhosis of liver without ascites	12	12	11	2
Malignancy of the liver—2°	3	3	2	0
Diffuse liver damage with jaundice directly after jaundice had subsided	3	3	3	1
Miscellaneous group: no clinical data suggesting liver damage, but reason to suspect it	15†	17	12	3
Total	33	35	28	6

* 5 mg. per kilo.

† Three of these cases, all of which were among the negatives, received 2 mg. bromsulphalein per kilo.

parative studies yielded 12 positive bilirubin and 3 positive bromsulphalein tests. In no instance was the bilirubin test negative when the bromsulphalein was positive. This becomes doubly significant in the face of the fact that in 30 of the 33 cases the dose of bromsulphalein intravenously administered was 5 mg. per kilogram—2½ times the amount originally advocated by its sponsors, Rosenthal and White.⁵ In 3 cases (in the Miscellaneous group), the 2-mg. dose was used. Retentions of bromsulphalein in excess of 10% at the end of ½ hour, as originally postulated with the 2-mg.

dose, were regarded as abnormal irrespective of the amount employed. Retentions of bilirubin in excess of 5% at the end of 4 hours were regarded as abnormal. Thus in a total of 33 cases in which 35 comparative tests had been made, 28 showed abnormal retention of injected bilirubin and 6 showed abnormal retention of injected bromsulphalein. It should again be emphasized that the bilirubin test is frequently positive in mild instances of liver damage. Hence the bilirubin excretion test is of value where the other tests usually yielded negative results.

The reasons for the increased sensitivity of this test are probably dependent on the following factors: (1) The excretory function of the liver is being measured by its ability to handle a substance which is normally manufactured by the body and normally excreted by the liver. (2) In a good many instances the excretory function of the liver is the first to be disturbed. Hence, the use of a physiological substance such as bilirubin seems to be the most sensitive index for appraisal. (3) The usual excretory tests for hepatic function are based on the selective activity of the liver to remove foreign products, as dyes, from the circulating blood stream and excrete them into the duodenum. However, this would appear to be only partly true, since there is some evidence to indicate that a dye such as bromsulphalein, when injected into the blood stream, is not removed by the liver in its entirety. At least a portion of it is phagocytosed by the reticulo-endothelial cells.⁶ On the other hand, injected bilirubin circulates freely and is excreted *in toto* by the liver, except in obstructive jaundice. In this condition, according to Kanner,⁷ the storage of bile pigment takes place in the reticulo-endothelial cells. Yet this is of no practical moment, since the bilirubin hepatic excretion test is not employed in the presence of a serum bilirubinemia in excess of 1 mg. %.

It is not to be inferred that the bilirubin excretion test is to be used to the exclusion of all other laboratory methods in determining hepatic activity. Even though we believe it to be the best single procedure, the apparent inadequacy of liver function tests is partly due to efforts to make one method a gauge for all of the manifold liver tasks. Much information of diagnostic and prognostic significance can be derived from the frequent use of a variety of procedures, due consideration being given to their indications and limitations.³

The method originally devised by Eilbot for the performance of the bilirubin liver function test is rather difficult and time-consuming. We have introduced certain modifications which have been previously described.^{8,9} In order to further simplify the performance of the test, we have constructed a series of standards which may be used in place of the colorimeter. The essential advantages of the standards are simplicity of performance and reduction of costs. The use of the colorimeter requires a certain amount of diligent

application and experience which may not be available to many physicians desiring to employ this test. The clinical results obtained with the standards compare quite accurately with those of the colorimeter (Table 2) and such differences as are noted are of no significance in interpreting the results.

TABLE 2.—COMPARATIVE COLORIMETER AND STANDARDS. BILIRUBIN RETENTION DETERMINATIONS.

Case.	Colorimeter, %.	Standards, %.	Difference, %.
1	14.2	18.0	3.8
2	28.5	32.8	4.3
3	17.5	19.2	1.7
4	4.0	4.0	0
5	24.1	24.0	0.1
6	11.5	15.3	3.8
7	25.1	28.2	3.1
8	18.2	18.4	0.2
9	47.1	54.0	6.9
10	17.8	13.1	4.7
11	7.0	8.0	1.0
12	13.4	11.0	2.4
13	16.4	16.8	0.4
14	20.1	19.1	1.0
15	2.5	3.1	0.6
16	18.5	18.2	0.3
17	18.1	15.5	2.6
18	5.7	7.5	1.8
19	0	0	0
20	0	0	0
21	22.8	24.8	2.0
22	14.8	13.6	1.2
23	23.2	20.3	2.9
24	4.2	5.0	0.8
25	14.2	18.0	4.2

Method. The method employed by us at present in the performance of this test is identical with that previously described,^{8,9} except in the final step, where the percentage of retention of the injected pigment is determined by matching the plasma against a series of standards. A total amount of bilirubin* equal to 1 mg. per kilogram of body weight (never is more than 70 mg. used) is dissolved in 15 cc. of a $\frac{1}{10}$ molar solution of sodium carbonate which has been previously brought to the boiling point and then allowed to cool to 80° C. The bilirubin dissolves completely and a clear iodine-colored solution is obtained. A control sample of oxalated blood is collected in a dry syringe to prevent hemolysis, and with the needle *in situ*, the bilirubin is then injected intravenously. Oxalated samples of blood are obtained from the other arm within 5 minutes and again 4 hours after the injection. The concentration of the bilirubin in the plasma is determined by means of the Ernst and Förster¹⁰ method. The plasma is precipitated by redistilled acetone, which is used in different concentrations, depending on the amount of bilirubin in the sample. Thus, with the control and with the sample taken after 4 hours, 2 cc. of acetone and 2 cc. of plasma are used while to 1 cc. of plasma of the specimen taken after 5 minutes, 4 cc. of acetone are added. After the plasma and acetone mixtures are shaken, the samples are centrifuged, filtered, and promptly matched against the standards. Except during actual readings, the acetone

* Bilirubin may be obtained from the Eastman Kodak Company at Rochester, New York, and from Hoffman-LaRoche, Nutley, N. J.

solution of bilirubin must be protected from the light. The final calculations are made as follows:

$$\begin{array}{lcl} \text{A (control specimen)} & \times 2 \text{ (dilution)} & = \text{A}' \\ \text{B (5-minute specimen)} & \times 5 \text{ (dilution)} & = \text{B}' \\ \text{C (4-hour specimen)} & \times 2 \text{ (dilution)} & = \text{C}' \end{array}$$

$$\frac{\text{C}' - \text{A}'}{\text{B}' - \text{A}'} \times 100 = \text{percentage retention of bilirubin.}$$

The standards* are prepared by making dilutions of potassium dichromate varying from 1 to 2000 to 1 to 10,000, a 1 to 2000 solution yielding a color identical with that of 1 mg. % of circulating bilirubin while a 1 to 10,000 equals 0.2 mg. %. Dilutions between these two extremes are made as follows:

$$\begin{array}{lll} \frac{1}{2000} = 1.0 & \frac{1}{2857} = 0.7 & \frac{1}{5000} = 0.4 \\ \frac{1}{2222} = 0.9 & \frac{1}{3333} = 0.6 & \frac{1}{6666} = 0.3 \\ \frac{1}{2500} = 0.8 & \frac{1}{4000} = 0.5 & \frac{1}{10,000} = 0.2 \end{array}$$

If a drop of hydrochloric acid is added to each standard tube, the tube may be kept indefinitely without fear of change in color. A retention of over 5% of the injected pigment at 4 hours is considered abnormal.

Care should be taken to avoid overheating the sodium carbonate solution, since thus a rather strongly alkalin solution is produced which may cause an uncomfortable reaction. In our experience in over 150 instances, this accident occurred twice. In both instances the patient complained of nausea and hot flushes. The reaction subsided after a few minutes. Proper caution must also be exercised to inject the material intravenously. Accidental extravasation into the surrounding soft parts produces localized pain, edema and tenderness, and, rarely, pyrexia. The constitutional reaction which occurred once in our experience subsided without residue within 48 hours. However, with such a weakly alkalin solution no sloughing occurs.

Summary. 1. The superiority of intravenously injected bilirubin as a means of determining the excretory hepatic function in cases where the serum bilirubinemia is not in excess of 1 mg. % has been pointed out. It seems to be more sensitive than any available single method for determining hepatic dysfunction.

2. The method has been further simplified by the preparation of standards in lieu of the colorimeter.

3. Its indications, precautionary measures and complications have been mentioned.

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HEPATIC INFARCTION IN MYELOGENOUS LEUKEMIA AND PERIARTERITIS NODOSA.

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THE object of this communication is to report 2 cases of hepatic infarction recently observed at autopsy. One of these occurred as a terminal complication of myelogenous leukemia, and is perhaps the only reported example of this lesion associated with leukemia. The other occurred in a case of periarteritis nodosa involving the hepatic arterial tree. The mechanical factors operating in the vascular bed of the liver in periarteritis nodosa will be analyzed and discussed together with the resulting acute and chronic effects on the hepatic parenchyma. Various features of hepatic infarction, reviewed in recent articles by Lund, Stewart and Lieber¹ and by Pass,² will be referred to only briefly, as they concern the cases under consideration.

Case Reports. CASE 1 (Jefferson Hosp. 1-534).—A. B., a white female, aged 30, was admitted to the hospital January 28, 1935 with myelogenous leukemia. The blood count showed a moderate grade of secondary anemia and 398,000 white blood cells per c.mm. of which 24% were myelocytes. The Wassermann and Kahn reactions on the blood serum were negative. The patient received attention in the hospital and in the out-patient depart-

ment. She responded fairly well to Roentgen ray therapy over the long bones during a period of 2 years. The spleen gradually enlarged to form a hard tender mass extending from the left costal margin to the symphysis pubis and 6 cm. to the right of the midline at the level of the umbilicus. According to the clinical record the liver was never palpated and there was no note regarding tenderness. She developed bronchopneumonia with pleuritis and died March 10, 1935.

Autopsy (14 hours postmortem): *Combined gross and microscopic diagnoses:* 1, chronic myelogenous leukemia; 2, leukemic infiltration and enlargement of spleen and liver; 3, hyperplasia of bone marrow; 4, bronchopneumonia with acute pleuritis, right lower lobe; 5, thrombosis of the mural endocardium of left ventricle and of the pulmonary, splenic renal and hepatic vessels; 6, infarction of the liver, lung, spleen and kidney.

The liver weighed 3180 gm. and was uniformly enlarged. It was firm, pale, yellowish-brown and friable in consistency. The normal markings were not visible. Several firm, slightly elevated areas were palpable beneath the capsule. On section these areas were dark reddish-brown and sharply defined. They varied somewhat in shape but were roughly rectangular; the largest measured 4 cm. in greatest length. There was extensive occlusion of the veins by soft gray, friable thrombi. Gross exploration of the branches of the hepatic artery showed no evidence of occlusion. It was impossible to distinguish between the small arteries and the veins. The gall-bladder contained a few cc. of colored bile and the bile ducts were patulous.

In the microscopic sections from the non-infarcted portion of the liver, thrombi were observed in approximately half the branches of the portal and hepatic veins and in a few of the sinusoids. The majority of the thrombi were fresh; others were liquefied in the center and organized around the periphery and a few were fibrosed and canalized. In this portion of the liver no thrombi were present in the central veins or in the branches of the hepatic artery. Myeloid and erythropoietic cells and megakaryocytes were numerous in the inner third of the hepatic lobules and in lesser numbers in the portal areas which were dense and fibrous (Fig. 1). The patent venous channels were dilated and filled with leukemic cells. The hepatic cells were degenerated and compressed in the inner portion of the lobule but were well preserved elsewhere.

The infarcts and immediately adjacent tissue showed thrombi in the veins as described above together with hyalinized structureless thrombi in several large intrahepatic branches of the hepatic artery. The infarcts were composed of confluent necrotic areas with four fairly distinct zones presenting minor variations in different areas. The central area of the infarct was pale, necrotic and coagulated (Fig. 2). Totally necrotic portal radicles and thrombosed branches of the hepatic artery and portal and hepatic veins were identified within this central area. The cords of necrotic hepatic cells were shrunken, granular and vacuolated and the sinusoidal spaces were widened. They contained imperfectly staining fibrin, outlines of hemolyzed erythrocytes and necrotic leukemic cells. Outside the central area the sinusoids contained a large amount of acidophilic granular debris together with basophilic nuclear particles. More peripherally there were many well preserved red blood cells in the tissue spaces and the sinusoids were filled with masses of well stained fibrin. This entire area was sharply demarcated from the surrounding tissue by an intense infiltration of neutrophils and actively phagocytosing mononuclears which filled the spaces formerly occupied by liver cords.

There was evidence of active regeneration in the surrounding parenchyma. The nuclei were enlarged, hyperchromatic and often multiple and several were observed in mitosis. The superficial areas of infarction were usually separated from the capsule of the liver by a narrow zone of viable hepatic cells and the overlying peritoneum was occasionally covered by an exudate.

SUMMARY—**CASE 1.** In the liver of a subject dead of myelogenous leukemia several fresh infarcts were found associated with thrombosis of the intrahepatic branches of the hepatic artery, portal vein and hepatic vein. The venous thrombosis was as extensive in the liver generally as in the areas of infarction. It was impossible to state whether the arterial occlusion was the result of embolism or thrombosis. Thrombi in the left ventricle of the heart and in the pulmonary veins constituted a possible source for emboli. On the other hand, occlusion of the hepatic artery may have resulted from widespread thrombosis which was a striking feature of this case.

CASE 2 (P. G. H. 28699).—C. M., white male, aged 44, entered the hospital December 30, 1934 with cyanosis and pain in the abdomen and extremities of a month's duration. There was a history of exposure to lead over a period of years and the patient had been treated for lead colic in 1920. The blood pressure was 200 systolic and 100 diastolic. The urine contained albumin, casts and sugar. The Kahn and Wassermann reactions on the blood serum were negative. There was moderate secondary anemia; the icterus index was 6 and the van den Bergh reaction was indirect negative. An exploratory laparotomy and cholecystostomy were performed January 4, 1935. The gall bladder was thickened and adherent to the under surface of the liver. The head of the pancreas was about 12 cm. in diameter, and the surface showed small areas of fat necrosis. Following operation the drainage bile was blood-stained, and purulent material was aspirated from the gall bladder. Death occurred 5 days after the operation.

Autopsy (1 hour after death): *Combined gross and microscopic diagnoses:* 1, periarteritis nodosa with diffuse proliferative, necrotic, inflammatory and thrombotic arterial lesions and multiple infarcts of the liver, gall bladder, pancreas, brain and adrenal glands; 2, chronic periportal hepatitis with parenchymal degeneration of the liver; 3, chronic cholecystitis with fibrinous serositis; 4, chronic interstitial pancreatitis and fat necrosis; 5, myocardial degeneration; 6, nephrosclerosis and nephrosis.

The liver weighed 1800 gm. There were several yellow gray and red areas, approximately 2 cm. in diameter, beneath the capsule in the anterior and inferior portions of the right lobe. On section, these areas were conical with the base directed toward the surface. Some were fibrous, others firm and cheesy and in a few the central areas contained yellowish liquified material.

The gall bladder measured 2.5 cm. in diameter, the wall 0.6 cm. in thickness; it contained a small quantity of purulent material. The mucosa was bright red and covered by a pyogenic membrane. Attempts to probe the cystic duct were unsuccessful. The other bile ducts including the ampulla of Vater were patulous.

Microscopically, the infarcts consisted for the most part of confluent nodules of necrosis with central pale areas surrounded and separated from each other by zones of inflammatory reaction (Fig. 3). The central area of infarction was well circumscribed and showed total coagulation necrosis with preservation of the structural outlines of all the tissue elements. The hepatic cells were shrunken and presented sharply outlined faintly basophilic nuclei embedded in pale granular, acidophilic cytoplasm containing small clusters of brown pigment granules. The bloodvessels contained acidophilic material resembling fibrin and the sinusoids were variously filled with imperfectly stained debris. Outside the central area cellular disintegration was pronounced, the sinusoids were packed with mono-



FIG. 1.—Liver. Case 1. Showing non-infarcted area with leukemic cells. ($\times 250$.)

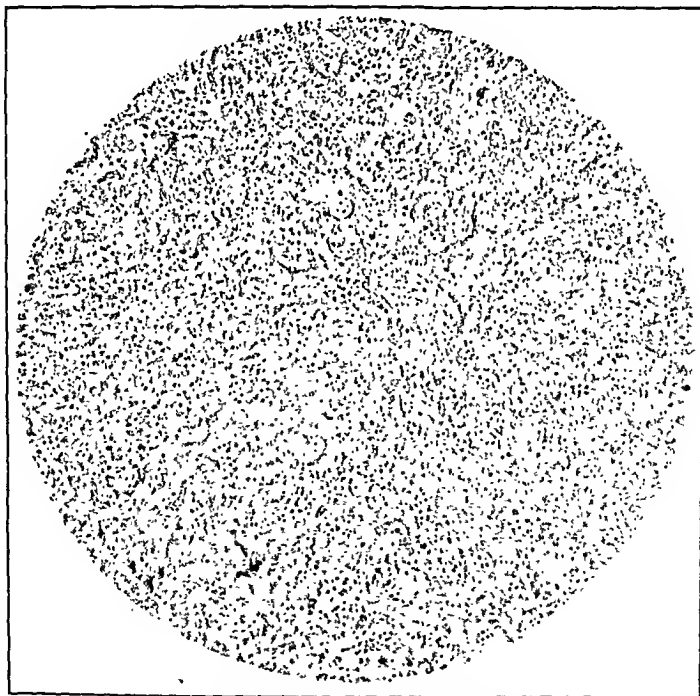


FIG. 2.—Liver. Case 1. Showing total necrosis of all tissue elements in area of infarction. The outlines of the leukemic cells are visible. ($\times 100$.) Contrast with Fig. 1.

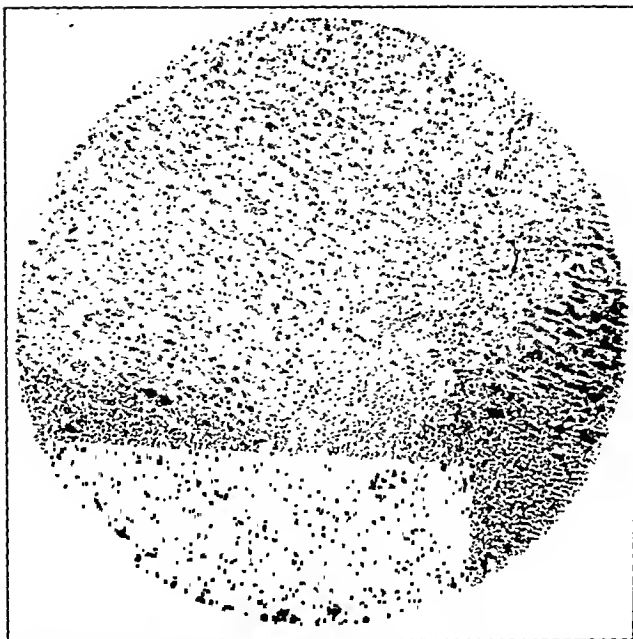


FIG. 3.—Liver. Case 2. Portion of infarct with pale central area and bordering zone of inflammatory cell infiltration. ($\times 100$.)

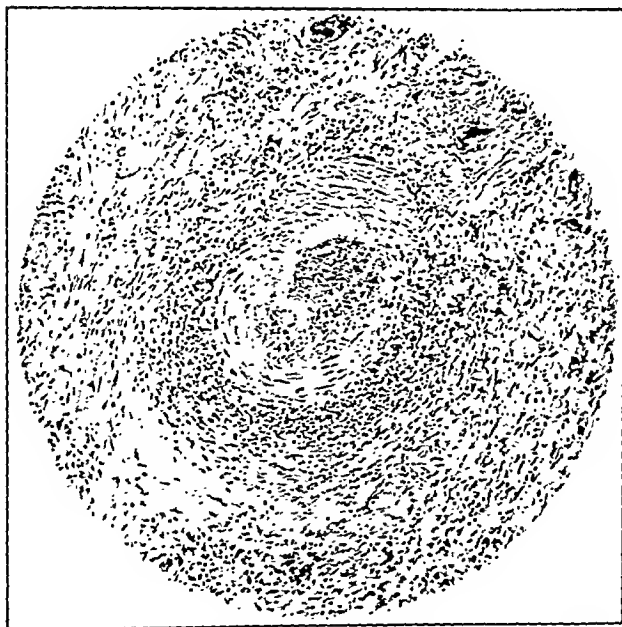


FIG. 4.—Branch of hepatic artery (Case 2) showing thrombosis and inflammatory changes of periarteritis nodosa. ($\times 100$.)

nuclear leukocytes and neutrophils and there was a large amount of basophilic nuclear material. This was surrounded by a zone showing a chronic proliferative reaction which blended superficially with Glisson's capsule. This area was composed of edematous granulation tissue, inflammatory cells, small proliferating tubular structures resembling bile ducts and scattered groups of viable hepatic cells.

Similar proliferative changes were noted throughout the liver generally, and many of the portal radicles were enlarged and fibrotic. In some areas, the picture resembled that of cirrhosis. Several large branches of the portal vein were thrombosed and fibrotic. The branches of the hepatic artery showed the characteristic changes of periarteritis nodosa with thrombosis of the lumen and necrosis and nodular areas of inflammatory reaction in and around the walls of these vessels (Fig. 4). The hepatic parenchyma not involved in the gross nodules of infarction was congested and contained microscopic areas of necrosis in parts of single and adjacent lobules.

SUMMARY—CASE 2. In a case of periarteritis nodosa, fresh, organized, bland and liquefied infarcts of the liver were observed in relation to occluded branches of the hepatic artery and portal and hepatic veins. There were also cirrhotic changes throughout the remainder of the organ.

Comment. The lesions which occur in the liver with periarteritis nodosa show marked variability in their morphology. The literature contains a number of reports of hepatic necrosis developing by this mechanism and certain of these fulfill all the requirements of genuine infarction. Arkin³ states that the presence of multiple infarcts in the liver in the absence of endocarditis should always call to mind periarteritis nodosa of the hepatic artery, and Pass² believes this condition to be the most common single cause of hepatic infarction. The finer ramifications of the arteries of the liver terminate as "end-arteries" within the substance of the organ and the collateral circulation of these vessels is extremely limited. Since the life of the hepatic cell is dependent upon an adequate supply of arterial blood, partial or complete occlusion of these vessels is followed by regressive changes of varying degrees.

Five cases of hepatic infarction in typical form occurring in periarteritis nodosa were found in the literature (Versé,⁴ Versé,⁵ Vanee and Graham,⁶ Gellerstedt and Wennerberg⁷ and Pass). In 10 other cases, lesions of the liver grossly interpreted as infarcts were reported (Christeller,⁸ Cases 2 and 3; Blum;⁹ Arkin, Case 3; Jäger;¹⁰ Weigeldt;¹¹ Kroetz;¹² Baló,¹³ Case 1; Harbitz;¹⁴ and Krahulik, Rosenthal and Loughlin.¹⁵ However, in the absence of detailed microscopic evidence, this diagnosis may be questioned. In 6 additional cases examined microscopically, none presented the characteristics of true infarction although their gross appearance was suggestive. These cases are of interest and may be cited briefly. In Longcope's¹⁶ case there were irregular, well outlined, slightly depressed red patches 0.5 to 2 cm. in diameter scattered over the cut surface of the liver from the periphery to the hilus. Microscopically these areas showed congestion and localized areas of

neutrophil infiltration. The liver cells were swollen and exceedingly granular. There were a few small foci of necrosis, with two or three vacuolated liver cells, granular and infiltrated with neutrophils. Marinesco¹⁷ described intense vascular lesions along the ramifications of the hepatic artery with small zones of fatty degeneration in the parenchyma. In Cameron and Laidlow's¹⁸ case "white infarcts" 4 by 3 cm. were found in the left lobe; microscopically these consisted of shrunken liver cells which were atrophic but not necrotic. The nuclei although imperfect in shape and staining, were fairly well preserved. Arkin's Cases 2 and 4 contained many irregularly outlined, reddish depressed areas; microscopically the liver parenchyma was destroyed leaving behind a vascular network filled with blood. In Mönckeberg's¹⁹ case, the cells in the periphery of the lobules were normal, those in the centers were fatty, degenerated and necrotic with infiltrated neutrophils. From the histologic data of the 6 cases just cited, it appears that none of these lesions should be regarded as true hepatic infarctions.

Chronic lesions of a diversified character also occur in combination with or independent of acute lesions, such as inflammation in and about the arteries, stasis, anemia, hemorrhage from rupture of an aneurysm (Friedberg and Gross²⁰), sinusoidal thrombosis and hepatic cell atrophy. The end results are fibrosis of the capsule, branched, diffuse or circumscribed fibrous scars corresponding to narrowed and obliterated arteries, perilobular and intralobular fibrosis, chronic interstitial hepatitis (Christeller, Case 2; Baló, Case 3; Elizalde and Di Pietro²¹; Friedberg and Gross); and in Arkin's Case 5, "hepar lobatum." This latter case is of particular interest. Four years prior to death the patient developed an acute attack of jaundice. At autopsy changes interpreted as late or healed periarteritis nodosa were found. The liver was small, coarsely granular and showed a number of deeply penetrating, depressed scars over which the capsule was wrinkled. The cut surface was traversed by connective tissue septa containing nodular, thickened and obliterated branches of the hepatic artery. Microscopic examination disclosed areas of unchanged liver tissue side by side with areas of marked congestion from which the parenchyma had disappeared. Arkin believed that the hepatic lesion was the result of periarteritis rather than the healed stage of yellow atrophy of the liver.

A number of mechanical factors influence the hepatic changes in periarteritis nodosa. Vascular occlusion may be abrupt or gradual, complete or incomplete in a single arterial branch. When gradual, sufficient time may elapse for the development of a collateral circulation but, during the interval, the parenchyma may suffer varying degrees of damage. Sudden complete occlusion by embolism or thrombosis may occur in a branch of the hepatic artery which was previously normal or was the seat of an incomplete occlusion the result of periarteritic lesions or aneurysm formation. A source for

emboli in such cases may exist locally in the proximal arterial tree or they may arise from thrombi in the pulmonary veins or left heart. Additional factors contributing to the production of vascular lesions in the liver of periarteritis nodosa are thrombosis of the branches of the portal and hepatic veins which is a common feature in this condition. In view of these factors the occurrence of diffuse, focal or intralobular necrosis, localized areas of congestion and hemorrhage and hepatic cell atrophy is readily understood. This also explains those changes described by some authors which are characterized by disappearance of hepatic cells in limited areas leaving behind a network of dilated sinusoids. This latter lesion, in various stages, resembles the "atrophic red infarct of Zahn" and the red areas described by Marchand in multiple nodular hyperplasia (subacute atrophy of the liver).

Infarcts of the liver occurring in periarteritis nodosa are frequently localized in areas already the seat of a well developed inflammatory reaction with its complicated enzymatic response. The action of heterolytic enzymes within these areas of necrosis may produce liquefaction, so that centers of infarcts may disintegrate with the formation of pus. The chronic hepatic lesions result, in part, from repair following inflammation along the bloodvessels, about infarcts, and in focal areas within the lobule. Fibrosis may also result from parenchymal changes produced by the pressure of aneurysms or periarteritic nodules. The progressive development of this combination of diversified changes may eventuate in a finely or coarsely granular liver with depressed scars on the surface not unlike that seen in cirrhosis.

Conclusions. 1. Two cases of hepatic infarction are described and illustrated. These occurred respectively in chronic myelogenous leukemia and in periarteritis nodosa.

2. A summary of the hepatic lesions occurring in the reported cases of periarteritis nodosa is presented and discussed, together with an analysis of the factors operating in the vascular bed of the liver and of the resulting effects on the parenchyma.

3. Periarteritis nodosa is the most frequent single cause of hepatic infarction.

4. The later stages of the necrotic and inflammatory processes of periarteritis nodosa resemble other cirrhotic processes.

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THE EFFECT OF OIL OF WINTERGREEN ON THE INCIDENCE OF SPONTANEOUS CARCINOMA IN MICE.*

IV. EFFECT ON GROWTH RATE AND SURVIVAL TIME AFTER ONSET OF MALIGNANCY.

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RECENTLY data were published^{1,2,3} which indicated that the true oil of wintergreen had a significant effect on survival time of mice harboring spontaneous cancer of the mammary gland. It was shown that if such mice had received daily small amounts of the oil in an otherwise standard oatmeal diet, they would live longer than their controls. This effect on survival time was cumulative;

* This experiment has been made possible by grants from the Josiah Macy, Jr., Foundation and the International Cancer Research Foundation. Acknowledgment is also given to Dr. A. H. Smith for his kindness in redistilling the commercial synthetic methyl salicylate (Eimer and Amend) used in this investigation. Dr. L. D. Francis determined that the oil weighed, on an average, 0.2265 gm. per drop (by medicine dropper).

that is, the longer the animal had been on the oil-oatmeal diet or the younger it had been placed on that régime, the longer it would live after the ensuing tumor had developed.

In order to test out further the action of the various components of the natural oil of wintergreen on malignancy, it became desirable to try the redistilled synthetic methyl salicylate on cancerous mice after they had developed spontaneous carcinomas of the mammary gland. For this study 32 mice of the A strain⁴ were employed. These were divided into three experimental groups and two control groups, according to Table 1.

TABLE 1.—SURVIVAL TIME OF MICE.

	No. of mice.	Average survival time in days.
1:1 MS	4	41.5
First control	7	51.8*
1:2 MS	7	54.7
Second control	7	59.3
1:3 MS	7	56.6

* One control animal lived 154 days of life after the onset of malignancy. For reasons given in the text, the calculation of survival time (prognosis) for the first group of controls is given on the basis of the 6 other mice used.

Four criteria of the possible effect of the oil on the tumor-host relationship was used. These were: 1, the growth rate of the tumor; 2, food intake; 3, total body weight; and 4, the survival time after the discovery of the tumor. All animals were kept under the same conditions. A single animal was kept in a cage. Food was given in a round glass dish over which was clamped a metal cover. A single hole approximately $1\frac{1}{4}$ inches in diameter had been punched in the center of the metal cover. The basic diet for the control animals was a mixture of Quaker rolled oats, Baugh and Sons best meat scrap, Klim powdered "gas packed" whole milk, and salt. The oil was added to this basic diet in three proportions. In the first experimental group, the oil was added in the ratio of 1 drop of oil (by medicine dropper) to 1 gm. of the oatmeal mixture (1:1 MS, Table 1). In the second experimental group the ratio of 1 drop to 2 gm. of food was used (1:2 MS, Table 1), and in the third group the ratio of 1 drop to 3 gm. of the oatmeal mixture was employed (1:3 MS, Table 1). The two groups of controls were alternated between the experimental groups in order to avoid undue sampling of mice with spontaneous tumors.

The results are given in a series of charts. Chart 1 gives the data on the growth rate of the tumors in the two control groups. These growth rates are calculated on the basis of the linear measurement, determined by calipers, along the greatest diameter. Measurements on the other two dimensions had also been taken but since these showed the same tendency, they are not included in this report. It does not seem desirable to attempt to reconstruct the size of the

tumor by taking into consideration the three dimensions at one time. Necrosis and hemorrhage into the tumor always interferes with determination of absolute size in the growing tumor.

Chart 1 shows that the growth rates for the two sets of controls are identical. For this reason, the two groups of controls are added together, as is shown by the solid line in Chart 3.

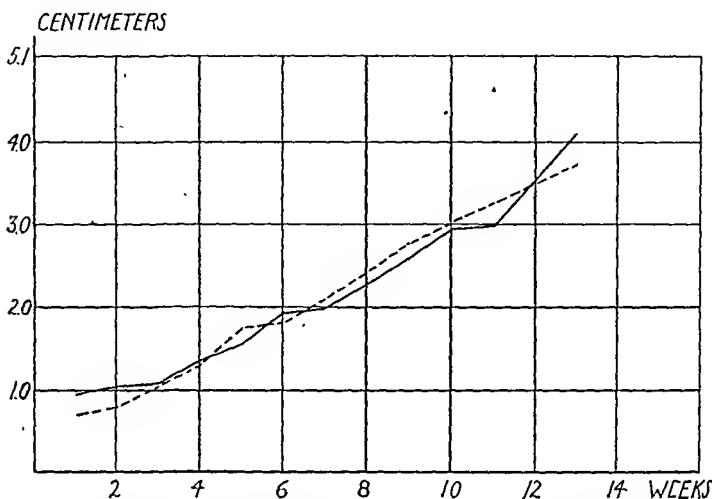


CHART 1.—GROWTH RATES OF TUMORS OF CONTROL MICE determined by linear measurement across the greatest diameter. Time in weeks is along the base line; linear measurement of the tumors in centimeters is given along the vertical line. Average growth rate of tumors for first group of controls is given on the solid line; the average growth rate for the second group of controls is given on the dash line.

Chart 2 gives the data on the growth rates (greatest linear diameter) for the tumors in the three sets of experimental (oil-treated) animals. The first group (1:1 MS) is given on the solid line; second group (1:2 MS) on the short dash line; while the third group (1:3 MS) is given on the dot and dash line. Since the rate of increase for the three groups is the same, we decided to add all experimental animals together. The difference between the three groups lies in the size difference of the tumors at the start of the experiment. The three experimental curves are added together and the resultant curve is given on the dash line of Chart 3.

Chart 3 gives the comparative data on tumor growth rates for the control and the experimental animals. For the first 8 weeks of growth the two curves are parallel, the experimental curve is slightly above the control group. This is due to the fact that the experimental mice had slightly larger tumors at the start of the experiment. Beyond 8 weeks, the curve for the experimental animals drops below that for the control mice.

Chart 4 gives the data on total body weight throughout the observation period. The data for the control animals are given on

the solid line; comparable data for the experimental animals are given on the dash line. It is seen that the control animals gradually increased in weight during the extent of the experiment; whereas

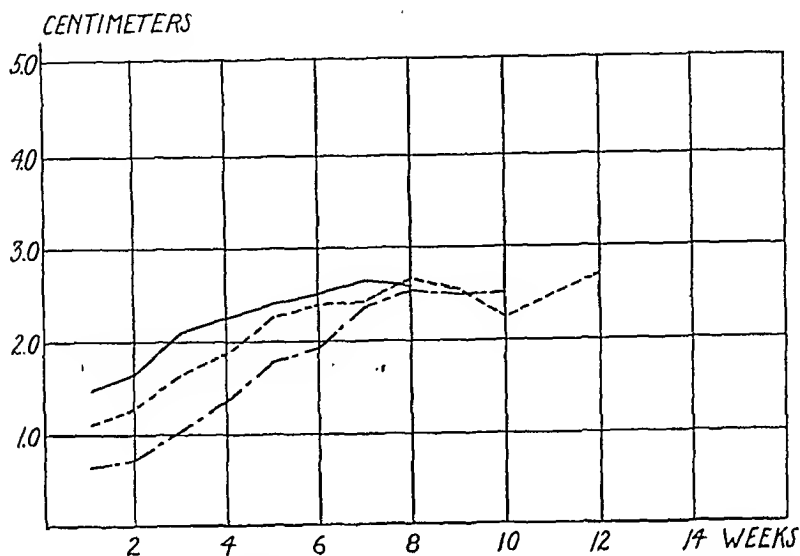


CHART 2.—GROWTH RATES OF TUMORS OF TREATED MICE. The first group of experimental animals (1:1 MS) is given on the solid line; the second group (1:2 MS) along the dash line, while the third group (1:3 MS) is given along the dot and dash line. Time in weeks is given along the base line; lineal measurement of tumor in centimeters is given on the vertical line.

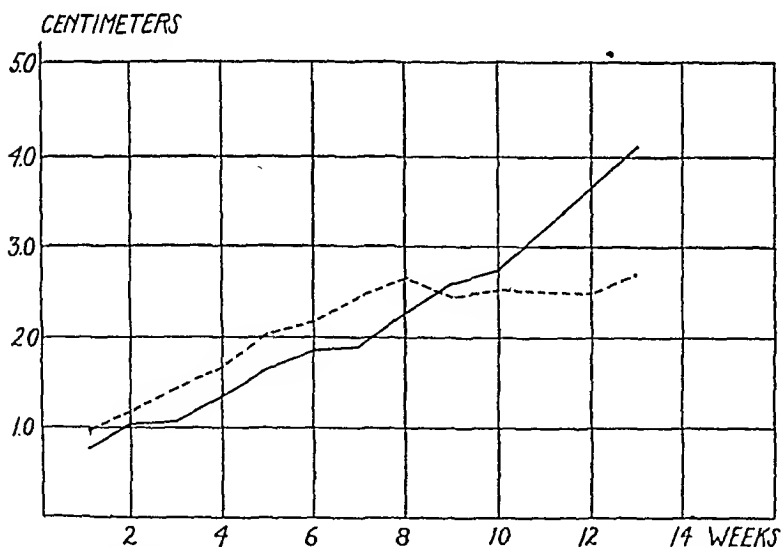


CHART 3.—COMPARATIVE DATA ON GROWTH RATES OF TUMORS. The control group is given on the solid line and the averaged three experimental groups on the dash line.

the experimental animals lost weight for the first 4 weeks. After that time the curve for the experimental group increased parallel to the control curve.

An attempt was made to ascertain the cause of the loss of weight on the part of the experimental group during the first 4 weeks. The first suggestion that seemed reasonable was the fact that the bitterness of the food (with the added oil of wintergreen) prevented the animal from eating sufficient quantities to sustain a standard body weight. Accurate determinations on the daily consumption of food for the experimental animals were obtained. For the first 2 weeks, this average food intake per mouse was 4.30 gm. per day; for the second 2 weeks it was 4.87 gm. per day; for the third 2-week period it was 4.41 gm. per day, and for the fourth 2-week period it was 5.25 gm. per day.

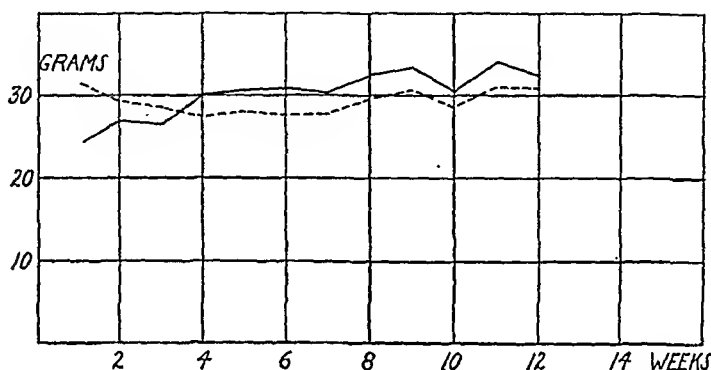


CHART 4.—TOTAL BODY WEIGHTS (MOUSE PLUS TUMOR). The control mice are given on the solid line; the experimental animals on the dash line. Time in weeks is given along the base line, weight in grams is plotted along the vertical line.

Comparable data for the control group was not available. With the equipment at hand, the control animals spilled so much food, that reliable data were not possible. It seems unlikely, however, that the administration of the oil interfered in the normal food eating habits of the mice.

Charts 5, 6, and 7 present the data on survival times of the mice after the onset of cancer for the experimental and control animals. Chart 5 gives the data for the control animals. For the first set of controls, the data are on the solid line; for the second group of controls the data are on the dash line. Since there is little difference between the two groups, the data are added together. The data for the combined control animals thus gave the curve on the dot and dash line. This average curve is also given on the solid line of Chart 7.

Chart 6 gives the data on the survival time for the second and third groups of experimental animals. Since only four animals comprised Group 1, a survival curve for this number is not significant. The average for the curves for the two groups of experimental animals is given on the dash line of Chart 7.

In the control groups was one animal that lived 154 days. Such an animal is extremely rare among the tumor mice of the inbred

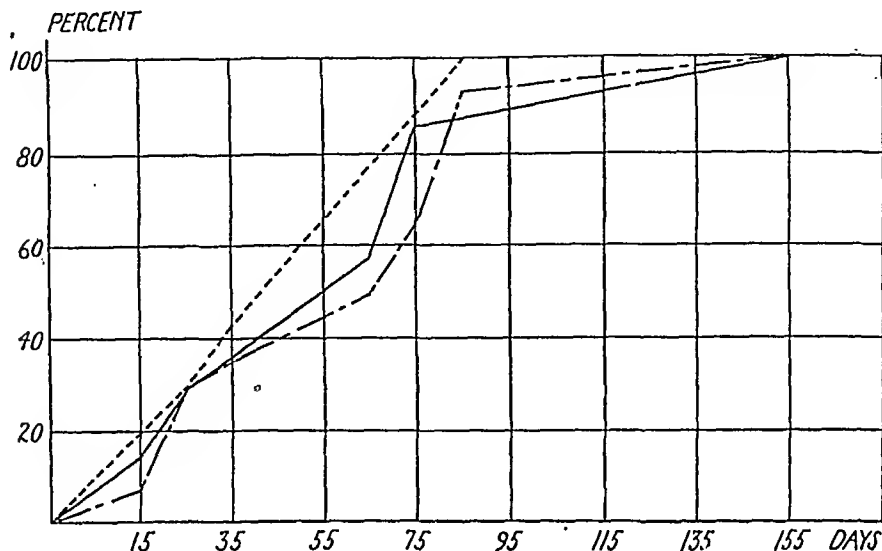


CHART 5.—SURVIVAL TIME OF MICE WITH SPONTANEOUS CONTROL TUMORS. The first group of controls is given on the solid line, the second group on the dash line. The average for the two groups is given on the dot and dash line. Time in days is plotted along the base line; percentage of dead mice is given on the vertical line. Successive points on the curves are therefore cumulative.

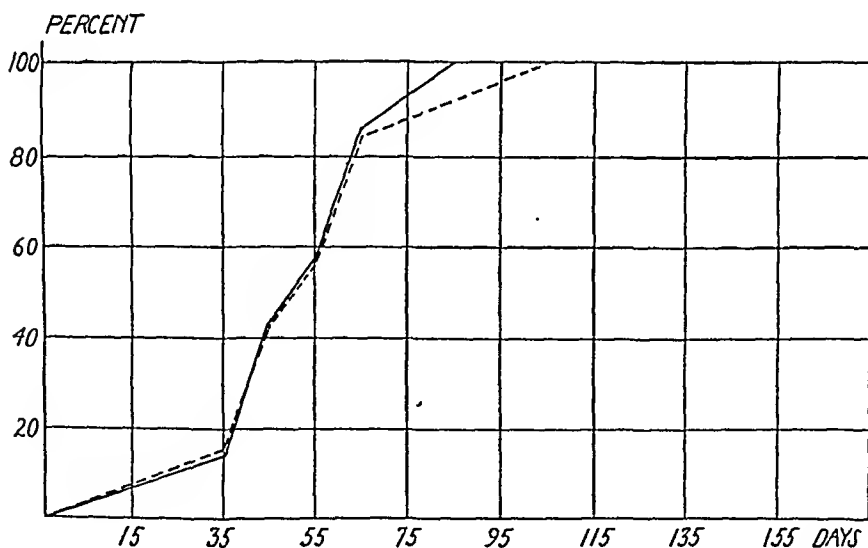


CHART 6.—SURVIVAL TIME (PROGNOSIS) FOR TWO SETS OF EXPERIMENTAL ANIMALS. Time in weeks is given on the base line; percentage of death is given on the vertical line.

strain used in this experiment. Consequently, we have deemed it wise to exclude it from calculations of survival time. When this is done, it is obvious that there is no difference between the survival

times for the experimental animals and the control groups (see Table 1 and Chart 7).

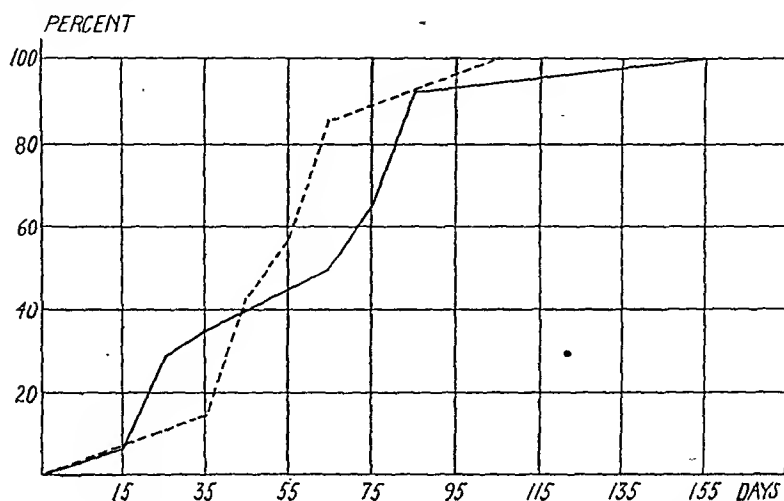


CHART 7.—COMPARATIVE DATA ON SURVIVAL TIME FOR THE TWO GROUPS OF MICE. The average survival time for the controls is given on the solid line; the survival time for the experimental animals is given on the dash line.

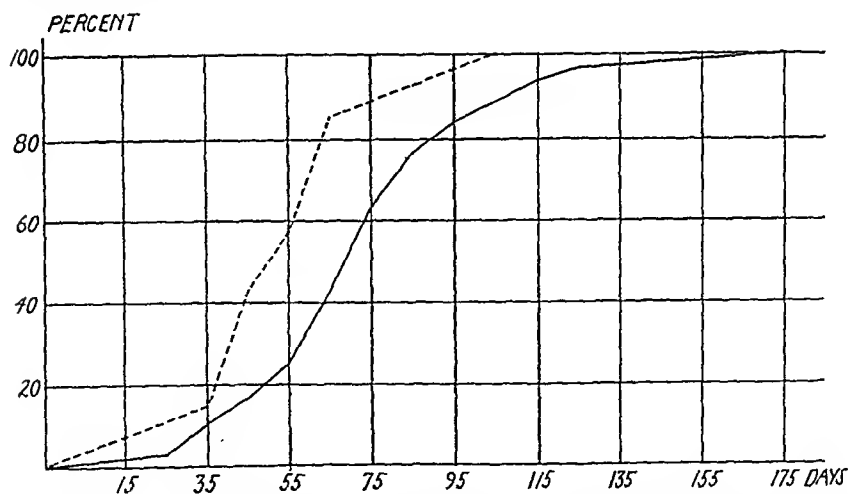


CHART 8.—COMPARATIVE DATA ON SURVIVAL TIMES. Survival times for experimental animals that had received daily small amounts of the natural oil of wintergreen before the onset of malignancy are given on the solid line, and for experimental animals that had been given synthetic methyl salicylate after the onset of the disease on the dash line.

Chart 8 gives (1) the data on the survival time of cancerous mice that have been put on an oil-oatmeal diet after the onset of the disease, and (2) data on the survival time of cancerous mice that had been put on an oil-oatmeal diet before the onset of the disease.³

Discussion. The daily administration of small amounts of the natural oil of wintergreen has had two effects on the incidence and severity of spontaneous carcinoma of the mammary gland.^{1,2,3} In the first place, the age at which spontaneous carcinoma of the mammary gland occurs has been delayed, and, in the second place, survival time of the animal harboring a tumor is also increased. This applies only to those animals which have been subjected to the treatment over a period of weeks or which were young mice at the start. The present study would indicate that the disease of cancer of the mammary gland cannot be influenced by the daily administration of redistilled synthetic methyl salicylate through the diet when treatment is started after the onset of malignancy. The slowing up of the growth rate of tumors in the experimental animals below the rate for the controls is probably due to earlier mortality of those mice which were growing the tumors at a more rapid rate.

Conclusions. 1. In order to influence malignancy, natural oil of wintergreen must be administered to young animals over a period of weeks before the condition arises.

2. Daily administration of the synthetic oil of wintergreen after the onset of cancer has no detectible effect on malignancy.

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CHRONIC DYSENTERY, DISTAL ILEITIS AND ULCERATIVE COLITIS.

A FOLLOW-UP OF THE JERSEY CITY EPIDEMIC OF BACILLARY DYSENTERY.

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ADEQUATE follow-up studies of acute bacillary dysentery may shed important light upon certain obscure intestinal diseases. With this purpose in mind, and in order to corroborate observations previously made upon sporadic cases, a 9 to 12 months' study was

instituted following the major Jersey City epidemic of 1934.¹ Inasmuch as only hospitalized patients were included in this investigation, centralized control was effected both during the epidemic period and the subsequent follow-up.*

TABLE 1.—CHRONIC SYMPTOMATOLOGY 9 TO 12 MONTHS AFTER AN ATTACK OF ACUTE BACILLARY DYSENTERY.

Total number of cases in original group . . .	210
Total number of cases in follow-up . . .	122
Persistent or recurrent symptoms and signs . . .	46 (37.7%)
Diarrhea with blood, mucus and pus . . .	8 (6.5%)
Watery diarrhea without gross blood . . .	12 (9.8%)
Bloody evacuations without diarrhea . . .	3 (2.4%)
Miscellaneous intestinal symptoms . . .	23 (19.0%)

TABLE 2.—VISIBLE EVIDENCE OF ULCERATIVE COLITIS OR ILEITIS IN FOLLOW-UP OF 122 CASES OF ACUTE BACILLARY DYSENTERY.
(13 Out of 122 Followed Cases.)

(a) Roentgenographic evidence of chronic ulcerative colitis . . .	8 (6.5%)
(b) Additional cases with sigmoidoscopic evidence of chronic ulcerative colitis . . .	2 (1.7%)
(c) Chronic distal ileitis (2 at operation, 1 at necropsy*) . . .	3 (2.5%)

* Almost entire ileum and all of colon involved.

Statistical Study of Chronic Intestinal Symptoms in 122 Cases. Of an original group of 210 patients we were able to secure the return of 122. Approximately 1 out of every 3 patients (37.7%) who were originally studied during the epidemic of 1934 had persisting or recurring symptoms and signs of intestinal involvement (Table 1). Diarrhea persisted in 20 instances (16.3%), 8 patients exhibiting gross evidence of blood, mucus and pus, 12 having watery bowel movements. Three additional patients (2.4%) had mucoid, bloody stools, but the daily frequency was not pronounced. Almost without exception recurring attacks of abdominal cramps were noted in the 23 cases (18.7%) referred to and, in addition, were present as the sole complaint in 8 others (6.5%). Intestinal spasm and tenderness in the right or left lower quadrants were present in almost all of the 46 cases with recurring or persisting symptoms. Roentgenographic evidence of chronic ulcerative colitis was obtained in 8 cases (6.5%) and sigmoidoscopic examination revealed lesions in the rectosigmoid in 2 more (1.7%). In all of the others clinical evidence pointed to lesions higher up in the colon, but permission for further examination could not be obtained. Two additional patients (1.7%) developed chronic distal ileitis with mesenteric lymphadenitis, proven at operation. In one instance the process involved the distal 20 cm. of ileum as well as the cecum and appendix. In the other the distal 40 cm. of ileum was affected. A third case (0.8%) was proven at necropsy. Almost the entire ileum and all

* We are indebted to Dr. George O'Hanlon, Superintendent of the Medical Center, for making these studies possible and to Dr. Louis L. Perkel for his cooperation in the roentgenographic examinations.

of the large bowel was the seat of a diffuse ulcerative lesion with inflammatory polyposis. There was a perforation in the transverse colon.

Discussion of Statistical Data and Their Significance. Leaving out of consideration all cases except those in which corroborative sigmoidoscopic, pathologic or roentgenographic evidence was obtained, it appears that approximately 10% developed chronic distal ileitis or ulcerative colitis by the end of the first year. The clinical and pathologic picture was distinctive and unmistakable and the initial infection was clearly due to *B. dysenteriae* (Flexner) in each instance. Careful investigation showed that in every case, although the original attack of acute bacillary dysentery subsided, it had never cleared up completely. The chronic manifestations were definitely a continuation of the original disease. Collateral studies indicate that, while in a certain percentage of these chronic cases *B. dysenteriae* may still be recovered after the lapse of a year or more, in the majority of them this organism cannot be found on repeated fecal cultures. It appears, moreover, that secondary intramural invasion by the enterococcus and *B. coli* occurs through the ulcerations originally caused by *B. dysenteriae*. This is associated with chronicity of the disease as, once established, intramural infection is persistent and difficult to eradicate. Pathologically, the intestinal manifestations of acute bacillary dysentery are those of an enterocolitis. Any part of the small or large intestine may be involved, often in a segmental fashion. There is a definite predilection, however, for the distal ileum and colon. The chronic lesions represent unhealed acute lesions both as regards location and pathologic character. Thus, chronic distal ileitis is always preceded by the distal ileitis of acute bacillary dysentery and the chronic ulcerative colitis or granulomatous lesion is the aftermath of a similar antecedent infection in the colon, independent of or concomitant with involvement of the small intestine. As previously noted by one of us (J. F.), the various stages were observed in individual cases from the onset of acute bacillary dysentery to the fully developed ileal or colonic lesion. The follow-up studies in the Jersey City epidemic afford further evidence in support of the common pathogenesis of these diseases.

From the clinical and public health standpoints certain relevant observations are perhaps significant. If chronic distal ileitis and chronic ulcerative colitis are the result of bacillary dysentery, it is quite evident that accurate diagnosis, prompt isolation and adequate treatment are essential. It is important to recognize the atypical forms, such as the appendicular type with acute distal ileitis and mesenteric lymphadenitis, asymptomatic, afebrile, constipated or meningitic. Antidysentery serum of high antitoxin content must be given within the first 24 to 48 hours to be effective. Frequent periodic surveys of all foodhandlers, particularly in institutions,

should be made as well as careful supervision of water and all food supplies.

Conclusion. If one may generalize on the basis of 122 cases of a total of 201 studied during and after a major epidemic, it may be said that in acute bacillary dysentery (Flexner) approximately 90% of the patients recover completely. The other 10% develop the chronic dysentery in the forms more generally known as distal (regional) ileitis or ulcerative colitis. The intractable nature of these diseases suggests that perhaps the most adequate form of therapy is the prevention of bacillary dysentery.

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THE APPEARANCE OF THE ELECTROCARDIOGRAM IN RELATION TO THE POSITION OF THE HEART WITHIN THE CHEST.

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It has been established that changes in the position of the body lead to changes in the 3 lead electrocardiogram which cannot be satisfactorily explained by the Einthoven equilateral triangle concept.^{1,2,3} This we have confirmed in the present study. Further information was obtained by observing the changes in the position of the heart and surrounding structures by Roentgen ray.

Procedure. Standard 3 lead electrocardiograms were taken on 7 normal subjects and 5 patients with right-sided pneumothorax (administered therapeutically for pulmonary tuberculosis).^{*} In addition, various leads over the chest were taken in 3 normal subjects using the left leg as the site of the second electrode as is the practice now in taking Lead IV.

Records were taken with the subjects in the following postures:

1. Lying on the back.
2. Sitting upright.
3. Lying on the right side.
4. Lying on the left side.
5. Lying on the abdomen.
6. Sitting up and leaning forward.
7. Resting on hands and knees.
8. Leaning over the edge of the bed with the head and trunk hanging down vertically.

^{*} We are indebted to Dr. M. Biesenthal for permission to study these latter patients.

With these postures the body was rotated on its sagittal axis, viz. postures 1, 3, 4, 5, and around an axis connecting both hip joints; viz. postures 1, 2, 6, 7, 8 and 5. In 1 of the normal subjects a 6-foot Roentgen ray plate of both the anteroposterior and lateral views was taken in each of the above postures.* The plates were taken with the subject holding his breath at mid-inspiration.

Discussion of Results. In Table 1 is summarized the effect of changing the body posture on the electrical axis. It is evident that the changes are not always consistent and do not coincide with what might be anticipated from the theory of the Einthoven equilateral triangle.

TABLE 1.—SHIFT IN ELECTRICAL AXIS WHEN POSTURE OF SUBJECT IS CHANGED.

Subject.	From lying on back to					From lying on right side to		From lying on left side to lying on abdomen.
	Lying on right side.	Lying on left side.	Lying on abdomen.	Sitting upright.	Sitting leaning forward.	Lying on left side.	Lying on abdomen.	
Normal								
1. Fri.	L	R	..	L	L	R	..	L
2. Ko.	?	R	..	L	L	R	L	L
3. Bl.	?	R	..	L	?	R	L	L
4. Fra.	L	R	?	..	?	R	..	L
5. Fre.	L	R	R	L	L	R	R	L
6. Ock.	R	R	?	..	?	?	?	L
7. Dre.	..	R	L	L	R	R	L	L
Having right pneumothorax								
1. Kle.	R	R	R	R	L
2. Hir.	R	R	?	..	L
3. Bag.	R	R	?	L	?	..	L	L
4. Ros.	R	R	L	..	L	..	L	L
5. Hey.	?	?	..	L	L	L

L = left axis shift (electrical).

R = right axis shift (electrical).

.. = no significant axis shift (electrical).

? = questionable axis shift (electrical).

In addition there were changes in voltage independent of axis shift, changes in the *P* wave, in *Q R S* contour and in the *T* wave as the body position changed. The contour and amplitude in the precordial leads also showed marked changes when the posture was altered.

It is obvious that these electrocardiographic changes must be due to changes in the position of the heart in the chest. The Roentgen ray plates (Fig. 1) showed that the position changes were a combination of:

* We are grateful to Dr. R. Arens for placing the facilities of the Roentgen ray Department at our disposal.

1, Rotation around an anteroposterior axis situated at the base of the heart; 2, rotation around a transverse axis situated at the base of the heart; 3, rotations around the sagittal axis of the heart running from the apex to the base; 4, displacement of the heart

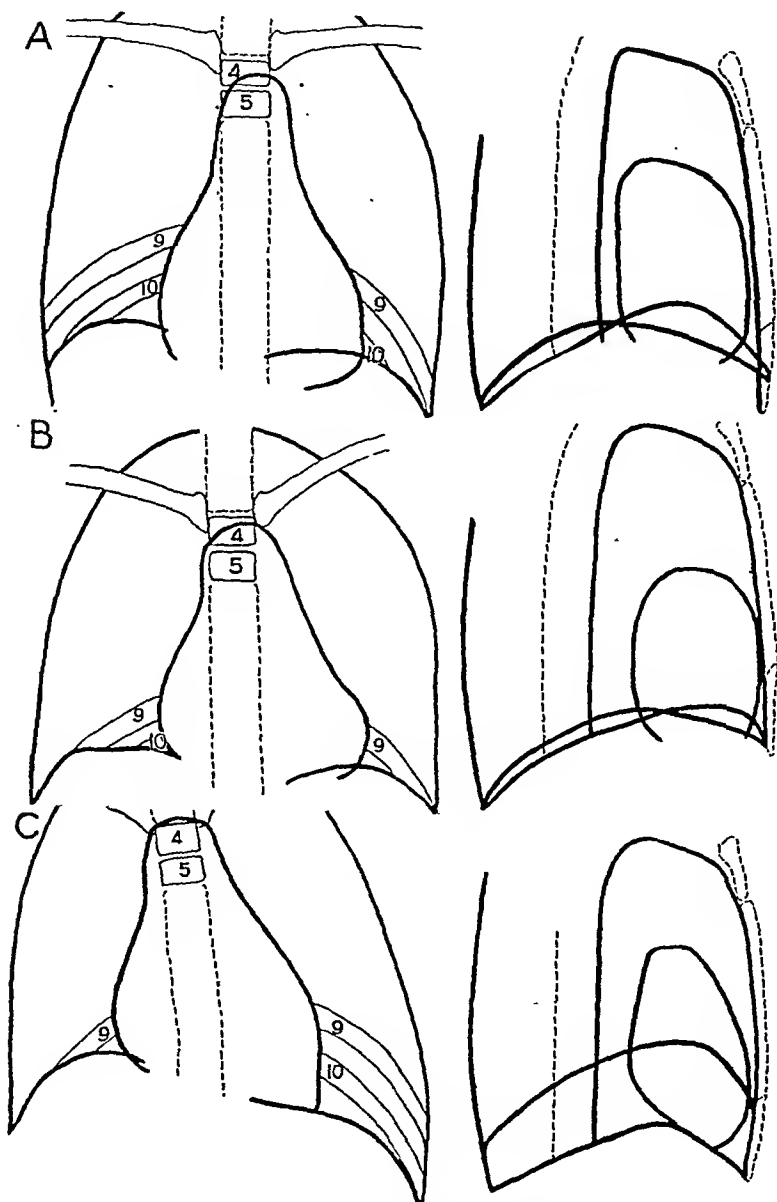


FIG. 1.—Tracings from 6-foot Roentgen ray plates of heart and chest of normal subject in different body postures. The anteroposterior views are on left; the lateral views on right of figure. Tracings A, taken with subject lying on back; B, subject sitting upright; C, subject lying on right side.

as a unit without rotation, and 5, alteration in the contour of the chest cavity.

The Roentgen ray plates also showed clearly that the right and left segments of the diaphragm as well as the anterior and posterior segments moved different amounts and sometimes even in different directions in different postures. Forward and lateral flexions of the vertebral column were also demonstrated in these plates.

The forces operating to bring these changes about are:

1. The action of gravity (*a*), pulling directly on the heart and rotating it around the 3 axes; (*b*), displacing the heart as a whole because the specific gravity of the heart is greater than that of the air-filled lung; (*c*), displacing the abdominal contents and consequently the segments of the diaphragm with which the heart is closely in contact.

2. The action of flexion and extension of the hip joint and the lumbar and thoracic vertebræ, the former varying the intraabdominal pressure and so the position of the diaphragm, the latter causing alterations in the shape of the chest cavity.

The net result of these changes is that the electrical field of the body is altered. In part this is due to the rotation of the electrical field of the heart around the sagittal and the transverse axes. The electrical field of the heart on its epicardial surface is not affected by these changes, but the relation of the body to this electrical field is altered.

Another more important factor modifying the electrical field of the body is the alteration of the regions of the heart in contact with the anterior chest wall, with the diaphragm and with the posterior paravertebral muscle mass, which the work of Katz and Korey⁴ has shown are good electrical conductors compared with the lungs which are poor electrical conductors. This latter change is in part due to displacement of the heart and in part to displacement of the lungs. As a result, different regions of the heart come in contact with these good conductors, and these good conductors come to occupy different parts of the wall of the chest cavity. The importance of this latter concept in explaining the electrocardiograms of pathologic hearts is being studied.

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PHYSIOLOGIC EFFECTS OF BENZEDRINE AND ITS RELATIONSHIP TO OTHER DRUGS AFFECTING THE AUTONOMIC NERVOUS SYSTEM.*

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IN the course of a group of studies on the drugs which affect the sympathetic and parasympathetic nervous systems, benzedrine was utilized as one of the sympathomimetic drugs. Its effects were so striking that a number of different types of observations were carried out. These are the subject of the paper which follows:

Benzedrine (phenylisopropylamine) is a synthetic preparation of the ephedrin and epinephrin group and belongs to the sympathomimetic class of drugs.¹ Most of the pharmacologic studies on benzedrine have been carried out on animals and have been mainly concerned with its effect on the blood pressure. Thus, Tainter,¹ Alles,² Hartung and Munch³ have described the marked and prolonged pressor effect of the drug in animals. Similar observations have been made by Piness and Miller.⁴ Clinically, benzedrine, like ephedrin, has been observed to have a marked decongesting effect on the mucous membrane of the nose, Eustachian tube and middle ear (Scarano,⁵ Bertolet,⁶ Byrne⁷ and Wood⁸). In an important clinical paper, Prinzmetal and Bloomberg⁹ have recently found that the drug is superior to ephedrin in the prevention of narcoleptic attacks.

This paper concerns a group of studies carried on for the purpose of adding pharmacologic and clinical data to the isolated observations hitherto reported. The other papers concern themselves, first, with the effect of benzedrine on the gastro-intestinal tract¹⁰ and, second, with its effect on the mood and sense of wellbeing of groups of normal and mentally sick individuals.¹¹

Material and Procedure. The subjects utilized in these experiments were mainly passive, submissive, unemotional cases of dementia præcox,

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who lay perfectly quiet throughout the entire procedure and whose general physical and physiologic states were known to us to be normal as a result of repeated and thorough studies. No preliminary anesthesia was used, thus eliminating an objectionable feature of the pharmacologic experiments done on animals. Eighteen patients, comprising 15 with dementia præcox, 2 with general paresis, and 1 with manic-depressive psychosis, were studied. These patients were brought to the laboratory without breakfast and allowed to rest for 15 to 30 minutes before the experiments were begun.

Benzedrine, given either orally, subcutaneously, or intramuscularly was administered either alone or in combination with other drugs, namely, sodium amytal, acetyl-Beta-methylcholin, and atropin. Its effects on the pulse, the blood pressure, the spinal fluid pressure, the basal metabolic rate, and the blood cellular constituents were studied. The effects of the drug on the gastro-intestinal tract and on the mood are the subjects of separate communications.

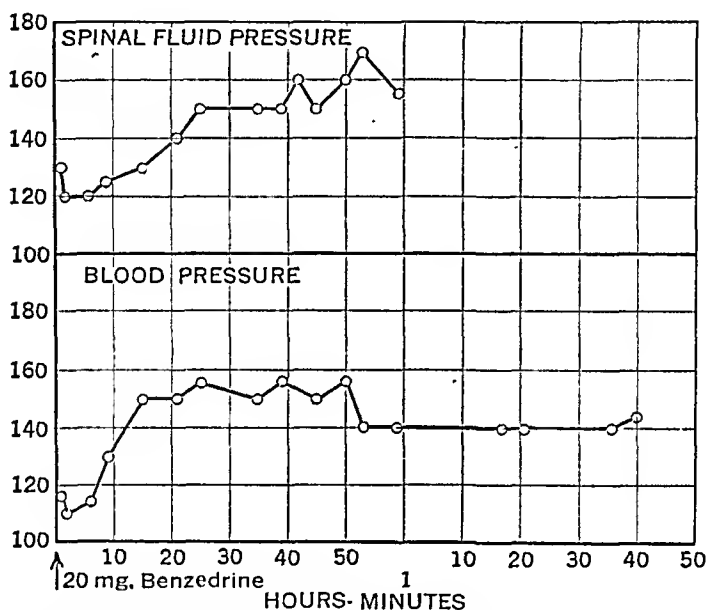


CHART I — Effect of benzedrine (20 mg. s.c.) on the systemic arterial pressure and the cerebrospinal fluid pressure.

1. SUBCUTANEOUS ADMINISTRATION OF BENZEDRINE (Table 1, Chart I). *Blood Pressure.* In 18 cases benzedrine was administered subcutaneously in doses of 9 to 50 mg. In every instance but one a gradual rise in systolic pressure, varying from 10 to 64 mm. of mercury took place. The rise in diastolic pressure was not commensurate with the increase in systolic pressure. No precise relationship between the change in blood pressure and the dose administered could be determined, although the larger doses in general brought about the greater rise. The blood pressure reached its maximum in from 11 to 85 minutes and gradually returned to its original level in 1½ to 7 or 8 hours.

Pulse. Simultaneously with the maximal increase in blood pressure, the pulse rate became diminished in 12 cases, remained un-

changed in 4 cases, and increased in 2 cases. The decrease in pulse rate varied from 4 to 25 beats per minute. Slight cardiac arrhythmia appeared in 4 cases; this was either of the sinus type or due to extrasystoles. During the rise in blood pressure, the pulse invariably became stronger.

TABLE 1.—EFFECTS ON THE BLOOD PRESSURE, PULSE AND SPINAL FLUID PRESSURE OF THE SUBCUTANEOUS ADMINISTRATION OF BENZEDRINE IN 18 SUBJECTS WITH MENTAL DISEASE.

Case.	Diagnosis.	Dose, mg.	Control period.			Height of reaction.			Time.
			B.P.	Pulse.	S.F.P.	B.P.	Pulse.	S.F.P.	
E. B.	D.P.	48	100/60	84	150	134/70	60	175	53 min.
J. B.	D.P.	20	120/60	76	80	150/64	64	115	16 min.
E. Ba.	D.P.	29	126/80	68	150	152/80	56	180	32 min.
D. F.	D.P.	39	114/70	80	150	148/72	88	190	46 min.
A. F.	D.P.	9	84/50	80	95	108/70	80	130	29 min.
M. G.	D.P.	20	116/70	84	135	156/90	76	175	50 min.
J. G.	D.P.	20	100/58	72	105	134/82	60	140	33 min.
H. H.	D.P.	20	110/72	92	150	120/78	92	190	19 min.
J. McK.	M.D.	40	136/72	88	145	200/100	64	240	1 hr. 30 min.
H. B.	G.P.	21	112/72	100	...	130/76	88	...	24 min.
H. H.	D.P.	20	126/80	80	...	156/86	76	...	23 min.
J. McG.	D.P.	30	122/64	100	...	172/90	88	...	51 min.
H. P.	D.P.	30	100/62	80	160	140/80	80	190	1 hr. 17 min.
A. McN.	D.P.	20	100/68	92	115	124/76	92	140	38 min.
F. H.	D.P.	40	130/68	84	125	160/86	64	155	
J. M.	G.P.	30	138/86	100	175	172/90	72	210	1 hr. 45 min.
J. R.	D.P.	40	130/80	108	...	126/70	120	...	40 min.
J. M.	G.P.	30	138/90	92	...	152/90	88	...	53 min.

D.P. = dementia praecox; G.P. = general paresis; M.D. = manic-depressive psychosis; S.F.P. = spinal fluid pressure in mm. of water.

TABLE 2.—EFFECT ON THE BLOOD PRESSURE AND PULSE OF THE ORAL ADMINISTRATION OF BENZEDRINE IN 14 SUBJECTS WITH MENTAL DISEASE.

Case.	Diagnosis.	Initial B.P.	Initial pulse.	B.P. at height.	Time.	Pulse at height.
J. C.	D.P.	126/70	80	160/82	46 min.	64
J. McG.	D.P.	126/70	92	160/80	1 hr. 20 min.	92
A. M.	D.P.	116/70	88	142/90	1 hr. 2 min.	90
J. B.	D.P.	126/70	100	134/80	49 min.	68
H. H.	D.P.	114/80	80	158/80	39 min.	84
F. H.	D.P.	126/76	80	150/40	40 min.	112
E. B.	D.P.	132/80	64	190/110	26 min.	52
A. F.	D.P.	100/66	72	122/70	2 hr.	64
H. B.	G.P.	120/78	84	148/82	52 min.	72
J. G.	D.P.	104/70	88	150/90	43 min.	84
C. P.	D.P.	130/96	84	164/92	1 hr. 40 min.	64
E. B.	D.P.	124/70	76	150/86	2 hr. 25 min.	56
J. P.	D.P.	120/70	96	140/80	1 hr. 12 min.	72
J. G.	D.P.	104/60	56	172/90	47 min.	52

Spinal Fluid Pressure. A uniform rise in the spinal fluid pressure was noted in the 14 cases in which it was followed. In 13 cases the increase varied from 25 to 40 mm. of water. In the other case it

rose 95 mm. This was in the subject who manifested the greatest rise in blood pressure. The maximal spinal fluid pressure occurred at about the time the blood pressure was at its height.

2. ORAL ADMINISTRATION OF BENZEDRINE (Table 2). Fourteen of the subjects were given 40 mg. of benzedrine by mouth and the blood pressure and pulse observed. There was a rise of blood pressure in every case, varying from 8 to 68 mm. of mercury. These figures are roughly similar to those observed in the same group of subjects when the drug was administered subcutaneously. With oral administration, however, in most instances the blood pressure reached its height more slowly, that is, in 20 minutes to 2 hours and 25 minutes. In the majority of instances the pulse rate diminished

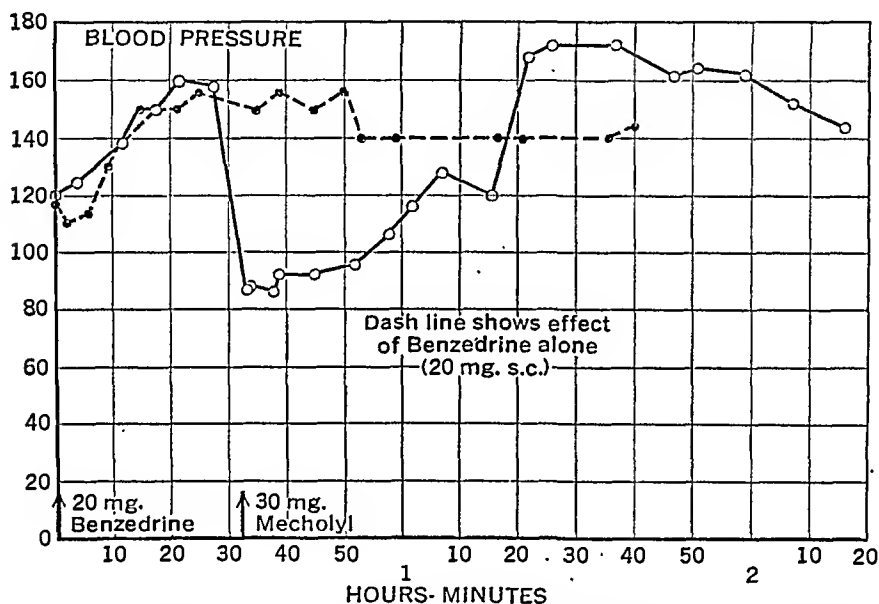


CHART II.—Effect on the blood pressure of benzedrine (20 mg. s.c.) alone and when followed by mecholy (30 mg. s.c.). It is seen that with subsidence of the mecholy effect, the benzedrine reaction continued unabated, the blood pressure returning to an even higher level than originally.

3. THE COMBINED EFFECT OF BENZEDRINE AND ACETYL-BETA-METHYLCHOLIN (MECHOLYL). Seven cases of dementia præcox were first given benzedrine subcutaneously in doses varying from 20 to 50 mg. The rise in blood pressure varied from 20 to 40 mm. of mercury and there was a drop in pulse rate varying from 2 to 16 beats per minute. When the blood pressure had reached its height, mecholy, an active parasympathetic stimulant, was administered subcutaneously in dosage of 20 to 30 mg. Within a few minutes following this injection, the blood pressure dropped sharply 36 to 96 mm. of mercury systolic and 20 to 54 mm. diastolic. Coincidentally with the marked fall in blood pressure there was a sudden rise in pulse rate in 6 cases, varying from 40 to 62 beats per minute.

In the other case there was a slowing of 12 beats per minute. The usual effects of mecholy, namely, flushing of the face, neck, chest, and back, lacrimation, salivation, rhinorrhea, and perspiration

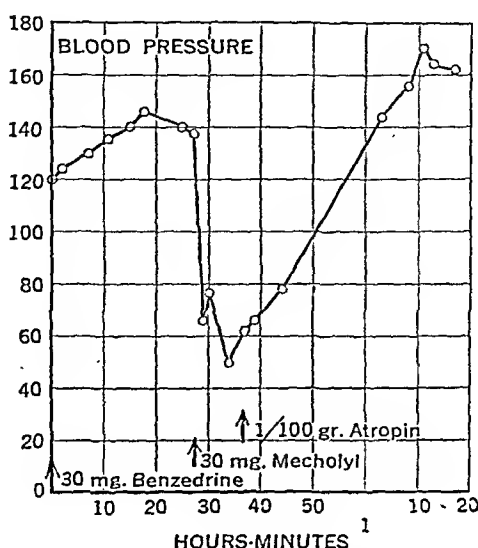


CHART III.—Effect on the blood pressure of benzedrine (30 mg. s.c.) followed by mecholy (30 mg. s.c.). The great fall in blood pressure produced by mecholy was quickly counteracted by atropin (gr. 1/100 s.c.), the blood pressure returning to an even higher level than that obtaining during the benzedrine reaction.

TABLE 3.—EFFECT ON THE BLOOD PRESSURE AND PULSE OF THE ADMINISTRATION OF BENZEDRINE (S.C.) AND MECHOLYL (S.C.) ON 7 DEMENTIA PRÆCOX SUBJECTS.

Case.	Diagnosis.	Control period.		Benzedrine.			Mecholyl.			Reaction at end of experiment.				
				Height of reaction.			Height of reaction.							
		B.P.	Pulse.	Dose (mg.).	B.P.	Time (min.).	Pulse.	Dose (mg.).	B.P.	Time (min.).*	Pulse.	B.P.	Time.†	Pulse.
M. G.	D.P.	120/80	80	20	160/100	28	68	30	86/54	6	112	172/100	1 hr. 37 min.	60
H. P.	D.P.	120/80	96	30	146/90	18	92	30	50/36	7	80	170/120	1 hr. 13 min.	112
J. P.	D.P.	142/80	84	40	170/100	47	80	20	134/80	1	120	152/80	1 hr. 41 min.	84
F. H.	D.P.	130/70	92	20	150/90	46	80	20	100/70	2	126	150/70	2 hr. 14 min.	68
J. McG.	D.P.	120/70	108	30	154/86	20	96	30	84/46	3	140	158/88	1 hr. 15 min.	68
J. B.	D.P.	126/68	84	40	156/80	19	68	30	94/60	1	112	156/80	1 hr. 17 min.	54
J. G.	D.P.	118/80	72	50	140/90	21	70	30	60/30	3	132	168/90	2 hr. 33 min.	48

* Time from the administration of the mecholy.

† Time from the beginning of the experiment.

occurred in varying degrees and differed in no essential manner from those reported by other experimenters and observed by us in another group of subjects. With the subsidence of the mecholy-

effects, which occurred within 10 to 30 minutes, there was a steady rise in blood pressure which finally, with but one exception, reached a height at least as great as that which had obtained at the height of the benzedrine reaction. The pulse was now slower in 5 of the cases than during the height of the benzedrine reaction. (Table 3, Charts II and III.)

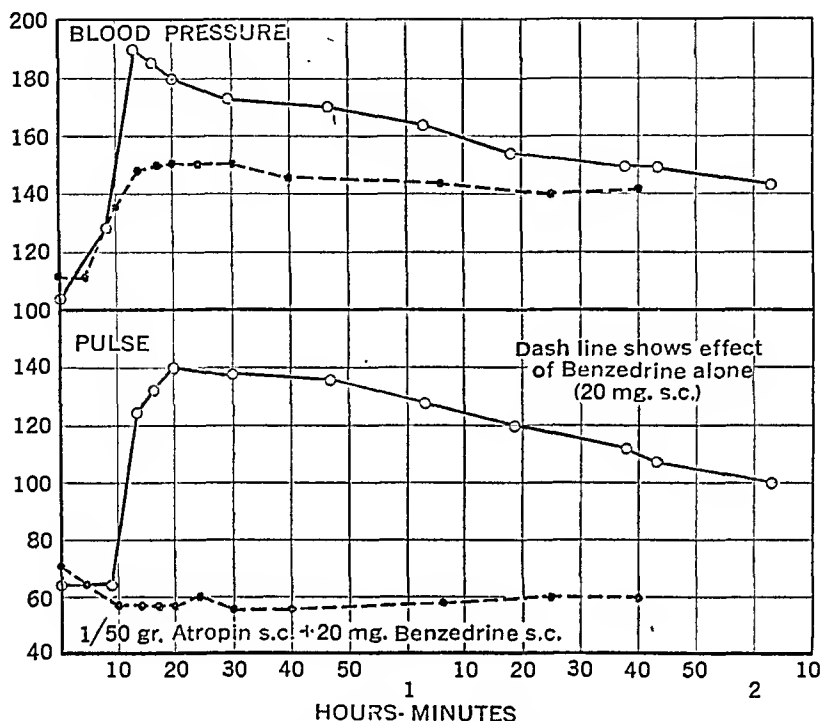


CHART IV.—Effect on the blood pressure of benzedrine alone and of benzedrine combined with atropin in the same subject a week later. It is seen that the combined effect of benzedrine and atropin produced a greater rise in blood pressure than that by benzedrine alone. This was probably due to an enhanced sympathetic effect when the parasympathetic system was paralyzed.

4. THE COMBINED EFFECT OF BENZEDRINE AND ATROPIN. Studies of the effect of atropin sulphate when given either together with benzedrine or just prior to it are now in progress, and the results cannot be given in detail. In 4 of 11 cases the rise in blood pressure was great, exceeding by far the rise obtained in the same patients when given benzedrine alone on previous occasions. (Chart IV.)

5. THE COMBINED EFFECT OF BENZEDRINE AND SODIUM AMYTAL.
A. *Benzedrine followed by sodium amytal* (Table 4, Chart V).

Benzedrine (20 to 50 mg.) was administered subcutaneously to 7 subjects. When the blood pressure had reached its maximum level, sodium amytal (.5 to .7 gm.) was injected intravenously. A sudden drop in pressure occurred reaching its lowest level soon after the completion of the injection of sodium amytal. The fall in systolic blood pressure varied from 4 to 40 mm. of mercury. All of the subjects fell asleep during the administration of the amytal. In 5

patients who were soundly asleep the blood pressure again rose and reached a level higher than that obtaining during the control period. In the other 2 cases the blood pressure was 8 to 10 mm. lower during the height of the amytal narcosis than during the control period. Although the depth of the narcosis did not appear to be affected, its duration, as compared with that occurring in a previously studied group of patients, appeared to be definitely shortened.¹² During the amytal narcosis, the pulse again increased in 5 cases and diminished slightly in the other 2.

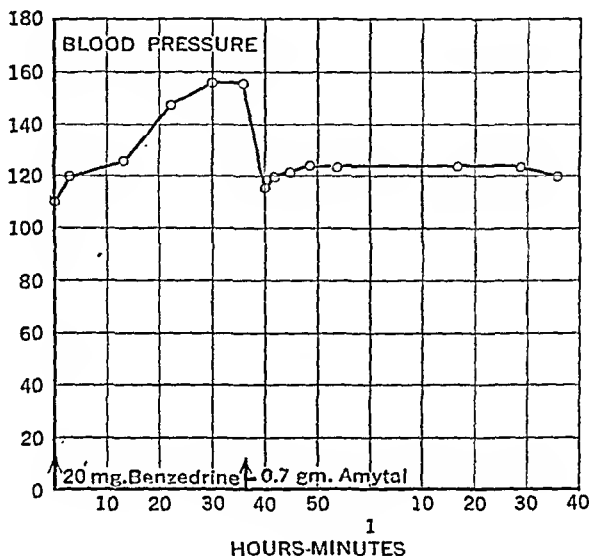


CHART V.—Effect on the blood pressure of benzedrine (20 mg. s.c.) followed by sodium amytal (0.7 gm. i.v.). The sodium amytal acted as usual to lower the blood pressure after a rise due to benzedrine. There was no fall in blood pressure below the original level.

If the reaction of the blood pressure to the injection of both benzedrine and sodium amytal is compared with that occurring to amytal alone, it will be observed that in the latter group the blood pressure returns to its original level in a longer period of time (Table 5). In other words, it appears that the effect of benzedrine, when given together with the amytal, was to shorten the blood pressure lowering period.

The spinal fluid pressure was observed in 5 of the above 7 cases (Table 4). In 2 cases it fell slightly during the amytal narcosis and at the end of the experiment returned to the original level. In the other 3 cases the spinal fluid pressure varied but slightly during the entire experiment.

B. Sodium Amytal Followed by Benzedrine (Table 6, Chart VI). Seven subjects received .5 to .8 gm. sodium amytal intravenously. At the completion of the injections, the fall in systolic blood pressure

TABLE 4.—EFFECT ON THE BLOOD PRESSURE, PULSE AND CEREBROSPINAL FLUID PRESSURE OF THE ADMINISTRATION OF BENZEDRINE (S.C.) FOLLOWED BY SODIUM AMYTAL (I.V.) ON 7 SUBJECTS WITH MENTAL DISEASE.

Case.	Diagnosis.	Control period.				Benzedrine, height of reaction.				Sodium amytal, height of reaction.				Reaction at end of experiment.			
		B.P.	Pulse.	S.F.P.	Dose, s.c. (mg.).	B.P.	Time* (min.).	Pulse.	S.F.P.	Dose i.v. (gm.).	B.P.	Time† (min.).	Pulse.	S.F.P.	B.P.	Pulse.	Time.†
J. M.	G.P.	136/84	84	...	40	158/100	50	128	...	0.7	146/100	5	120	...	168/100	128	1 hr. 10 min.
M. G.	D.P.	114/80	84	120	20	160/96	19	76	120	0.5	130/84	55	72	110	140/80	70	2 hr. 42 min.
E. B.	D.P.	110/70	72	80	20	156/96	30	56	80	0.7	116/80	4	72	65	120/88	56	1 hr. 35 min.
E. B.	D.P.	104/66	88	140	40	130/80	44	85	160	0.6	114/78	5	112	150	124/80	100	1 hr. 50 min.
F. H.	D.P.	106/60	76	130	30	138/80	40	68	125	0.7	134/82	19	76	140	124/76	72	1 hr. 44 min.
F. H.	D.P.	130/68	84	125	40	160/86	49	64	150	0.6	120/70	3	84	135	148/80	60	2 hr.
H. P.	D.P.	120/84	108	...	50	148/82	50	84	...	0.7	118/86	6	120	...	144/90	100	2 hr. 30 min.

* Time from benzedrine injection.

† Time from beginning of amytal injection.

‡ Time from beginning of experiment.

TABLE 6.—EFFECT ON THE BLOOD PRESSURE, PULSE AND CEREBROSPINAL FLUID PRESSURE OF THE ADMINISTRATION OF SODIUM AMYTAL (I.V.) FOLLOWED BY BENZEDRINE (S.C.) ON 7 SUBJECTS WITH MENTAL DISEASE.

Case.	Diagnosis.	Control period.				Sodium amytal, height of reaction.				Benzedrine, height of reaction.				Reaction at end of experiment.			
		B.P.	Pulse.	S.F.P.	Dose, i.v. (gm.).	B.P.	Pulse.	S.F.P.	Time* (min.).	Dose, s.c. (mg.).	B.P.	Pulse.	S.F.P.	Time† (min.).	B.P.	Pulse.	Time.†
H. H.	D.P.	130/90	92	165	0.7	90/70	96	190	17	20	136/90	96	150	20	128/86	92	1 hr. 12 min.
H. B.	G.P.	110/70	104	180	0.7	68/50	100	150	4	30	90/50	80	160	38	88/54	84	1 hr.
J. B.	D.P.	114/60	92	90	0.7	78/56	84	100	19	20	124/70	76	100	33	106/74	80	1 hr. 40 min.
J. G.	D.P.	102/60	84	25	0.6—0.7	68/46	64	25	3	20	130/76	52	100	50	116/80	50	1 hr. 25 min.
F. B.	D.P.	128/90	72	...	0.7	98/66	68	...	4	40	188/114	52	...	45	168/106	56	2 hr. 40 min.
J. McG.	D.P.	132/70	100	...	0.8	110/68	88	...	5	30	142/96	84	...	28	134/88	88	2 hr. 19 min.
H. G.	D.P.	128/82	72	...	0.6	88/68	88	...	4	30	160/106	68	...	43	148/98	68	2 hr. 7 min.

* Time from beginning of amytal injection.

† Time from beginning of benzedrine injection.

‡ Time from beginning of experiment.

varied from 16 to 42 mm. of mercury. Benzedrine in doses varying from 20 to 40 mg. was now administered subcutaneously. Within 5 to 10 minutes following this injection, the blood pressure in 6 cases began to rise, reaching a level at least as high as the original one within 21 to 41 minutes. In the other case the blood pressure slowly rose after an original drop from the injection of amytal, but did not reach the original level. Although the depth of narcosis did not appear to be affected by the benzedrine, its duration seemed to be definitely shortened as compared with a group in which amytal alone had been given.

TABLE 5.—EFFECT OF THE ADMINISTRATION OF SODIUM AMYTAL (i.v.) ON 12 SUBJECTS WITH MENTAL DISEASE. COMPARE THE BLOOD PRESSURE RESPONSE TO THAT SHOWN IN TABLES 4 AND 6 (COMBINED EFFECT OF SODIUM AMYTAL AND BENZEDRINE).

Case.	Diagnosis.	Dose, i.v. (gm.).	Control period.		At height.				At end.	
			B.P.	Pulse.	Time.	B.P.	Pulse.	Time.	B.P.	Pulse.
H. H.	D.P.	1.0	106/64	96	12 min.	90/70	96	4 hr. 13 min.	96/64	76
H. B.	G.P.	0.3	102/66	74	29 "	78/44	80	1 hr.	90/64	74
C. P.	D.P.	0.3	158/88	60	10 "	110/60	58	1 hr. 7 min.	110/60	58
J. N.	M.D.	0.25	110/44	72	41 "	88/38	60	1 hr. 9 min.	102/40	56
J. B.	D.P.	0.25	110/50	60	30 "	90/40	60	1 hr.	98/50	72
E. B.	D.P.	0.2	130/60	80	30 "	108/68	60	1 hr.	114/64	60
C. P.	D.P.	0.2	140/82	66	40 "	120/80	60	1 hr.	132/76	60
G. D.	G.P.	1.0	144/64	90	47 "	90/54	90	1 hr. 7 min.	92/56	90
G. T.	G.P.	0.8	120/60	84	21 "	94/50	76	1 hr. 11 min.	96/56	72
C. Pe.	D.P.	1.0	122/70	92	33 "	82/	96	1 hr. 12 min.	98/60	78
H. P.	D.P.	1.0	100/56	72	16 "	84/50	72	1 hr.	98/56	66
J. B.	D.P.	1.0	124/64	..	1 hr. 1 min.	80/66	..	1 hr. 26 min.	98/60	..

The pulse rate became diminished in 5 cases. In the other 2 cases a slight rise occurred following administration of sodium amytal. During the benzedrine reaction the pulse dropped to a still lower level in 6 of the cases. At the end of the experiment the pulse was slower in all but one of the cases than it was during the control period. The spinal fluid pressure showed no consistent variations.

6. OTHER STUDIES. *A. Hematology.* Studies of the hemoglobin, red cell count, white cell count, and differential count of the white cells were made in a group of 15 patients before and after administration of benzedrine. The following techniques were used: Hemoglobin was determined by the Sahli method, calibrated against the Van Slyke-Neill oxygen capacity method so that 100% equal 15.5 gm. of hemoglobin per 100 cc. In addition, the hemoglobin concentration was determined in each individual by the oxygen capacity method at the beginning of the experiment, once during its course,

and once at the end of the experiment. The erythrocyte and leukocyte counts were performed with standardized pipettes and hemacytometers, the same apparatus being utilized throughout the experiments. The hematocrit determinations were made with heparinized blood utilizing the hematocrit tubes of Wintrobe, the centrifuge speed being 3000 revolutions per minute, complete packing occurring in 30 minutes. The effects of the drug were quite variable, although in several instances striking. In 4 of the cases studied the red cell count rose 1.5 to 3 millions per c.mm. within 2 hours after administration of the drug without, however, any definite rise in hemoglobin. In 7 other cases the red cell count rose about

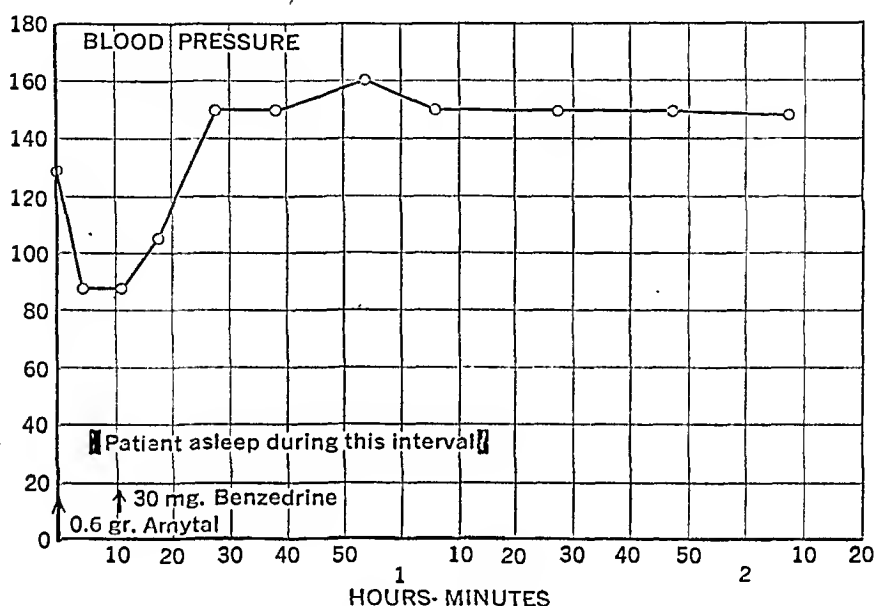


CHART VI.—Effect of sodium amytal (0.6 gm. i.v.) followed by benzedrine (30 mg. s.c.). The fall in blood pressure caused by the sodium amytal was soon counteracted by the benzedrine so that the blood pressure rose even higher than its original level. Although the depth of the narcosis is not disturbed by the benzedrine, the duration of the anesthesia is definitely shortened.

1 million. The leukocyte count became doubled, tripled, and even quadrupled in 4 of the cases; this was associated with a striking polymorphonuclear leukocytosis, although there was no increase in immature cells. In the other cases there was slight or moderate increase in white cells with an almost invariable increase in neutrophils. In 2 cases in which venous blood cell counts were compared with those of the peripheral blood, there was close agreement indicating that the observed findings were not due merely to changes in the peripheral circulation. There was no definite observed correlation between the extent of the blood pressure rise and that of the blood cellular constituents, nor could we predict in which patient a striking rise would take place (Chart VII).

Two subjects, who had shown a rather marked rise in red cell count, were given daily injections of benzedrine. In both, a steplike progression in red cell count occurred, so that at the end of 4 days

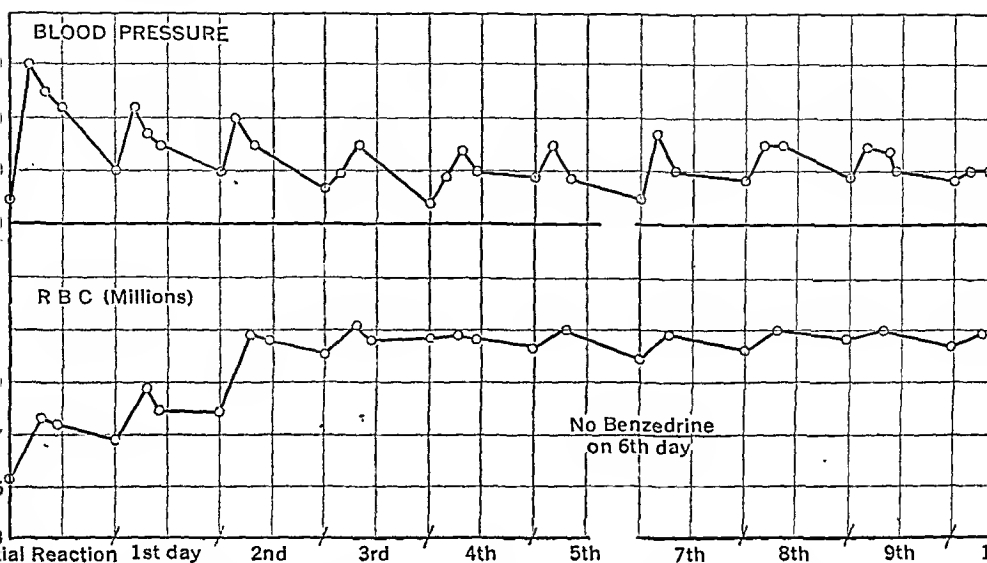


CHART VII.—Effect on the blood pressure and red blood cell count of benzedrine (40 mg. s.c.) given daily. The red count rose in steplike progression from a normal count of 5.3 millions to 10.9 millions in 4 days, remaining at about that level for 6 more days. The blood pressure showed less and less reaction until on the 10th day no rise occurred.

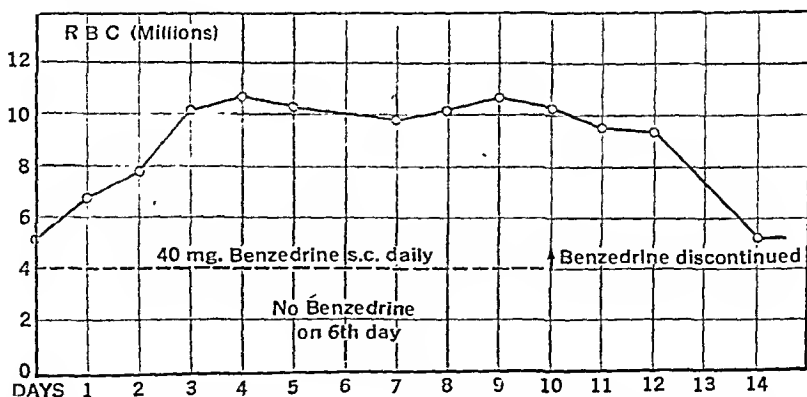


CHART VIII.—Same subject as in Chart VII. The benzedrine was discontinued on the 10th day and the red blood count gradually fell, reaching its original level on the 14th day.

the erythrocytes numbered respectively 9.3 and 10.9 millions per c.mm. There was only slight corresponding increase in hemoglobin and volume of packed red cells, however, indicating possibly that a number of very thin, red cells were present in the circulation. Further

studies of this interesting phenomenon are being carried out and will be the subject of another report (Chart VIII).

B. Effects on Metabolism and Sugar Content of Blood. The basal metabolic rate was studied before and during benzedrine. No significant changes were discovered, despite the fact that patients who could give an adequate account of their reactions stated that they felt somewhat flushed after taking the drug. No change occurred in the carbohydrate metabolism as indicated by the lack of rise in the blood sugar when the drug was given.

C. A special study of the effect of benzedrine on the *tonus and motility of the gastro-intestinal tract* is at present in progress. It suffices to say at this point that benzedrine exercises a greatly relaxing effect upon spasticity. An account of these phenomena appears in another paper.

D. In another paper a clinical account is given of the effect of benzedrine upon *fatigue and depression* in certain patients seen in hospital and private practice. At this point it will suffice to say that in the normal individual benzedrine exercises a striking effect in dissipating the sense of fatigue together with the mild depressed feeling which is frequently present. The effects of the drug are noted within a few minutes after oral administration and persist for several hours. If taken within a few hours of bedtime, the effect is to banish sleep entirely. This is quite in line with the observations made by Prinzmetal and Bloomberg in narcolepsy.

Discussion. The effect of benzedrine on the blood pressure of subjects with mental disease appears to be similar to that reported by other observers working on animals and man. There was no apparent change in the mental reactions of the subjects observed, although it was difficult or impossible in these patients to elicit any subjective manifestations of the drug. The effects of the drug on the symptoms of fatigue and depression in various clinical studies are discussed in an accompanying article.

That benzedrine produces a central stimulating effect is indicated by its efficacy in narcolepsy, its ability to arouse animals from barbitol anesthesia, and by the fact that it shortens the period of sodium amytal narcosis, as indicated in the present study.

The rise in cerebrospinal fluid pressure in most cases may indicate a slight increase in cerebral venous pressure or a slight cerebral vasodilatation, although there is, at the same time, a general vasoconstrictor effect of the drug. In a few cases the failure of the cerebrospinal fluid pressure to rise, even in the presence of a moderate rise in arterial pressure points to an unchanged diameter of the cerebral vessels. A rise in arterial pressure, occurring either with slight or no change in cerebral vessel diameter indicates, as pointed out by Gibbs and his co-workers¹³ and by Loman and Myerson^{14,15} an increase in cerebral blood flow. Benzedrine is thus similar to adrenalin in its vascular effects, although the latter drug acts more rapidly and

actively. It is unlikely, however, that an increase in cerebral blood flow explains the cerebral stimulating effect of the drug. The central effect of benzedrine appears to be due to some direct chemical action on the brain.

The reactions following the combined administration of benzedrine and mecholyl or atropin allow one to study the effects of simultaneous stimulation or depression of the sympathetic and parasympathetic systems. It is observed that the parasympathetic stimulating effects of mecholyl do not counteract or balance the sympathetic effects of benzedrine, but that the two drugs result in sharply distinct individual reactions. Thus, all the usual effects of mecholyl occur and have about the same duration as when this drug is administered alone. When the mecholyl reaction is spent, the effect of the benzedrine continues undisturbed. This is in contrast to the combined effect of epinephrin and mecholyl, since the effects of epinephrin are short-lived, whereas the effects of benzedrine are present for hours.

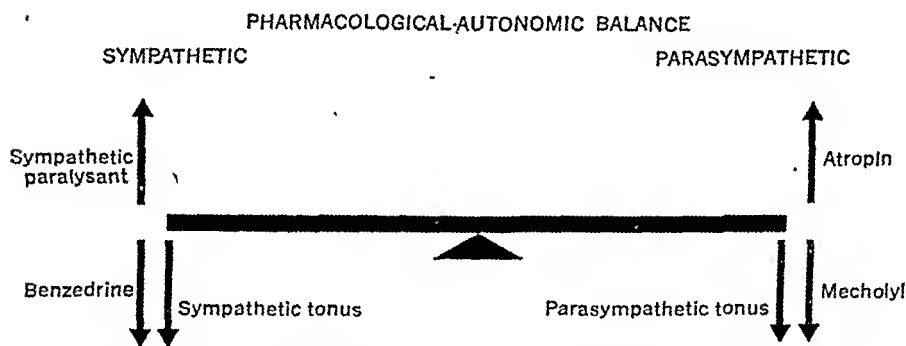


FIG. 1.—Schema of antagonistic activity of sympathetic and parasympathetic systems conceived as forces acting at opposite ends of a balanced lever.

Paralysis of the parasympathetic system by the use of atropin apparently enhances the action of the sympathetic stimulant, benzedrine. This suggests a constantly active system of "checks and balances" existing between the sympathetic and parasympathetic systems (Fig. 1). When the sympathetic is stimulated, as by benzedrine, a complete effect may not be obtained because of the continued activity of the parasympathetic. When, however, the latter system is paralyzed, as by atropin, the complete effect may occur. The remarkable effects of these various drugs on the circulation suggest that by methods of neuro-pharmacologic equilibration, it might be possible to exert dramatic clinical effects with their proper use.

A similar qualitative effect is seen when sodium amytal is given at the height of the benzedrine reaction. Although a drop in blood pressure follows the administration of sodium amytal, the blood pressure returns to its original or a higher level under the effect of

the benzedrine and in a much shorter time than it would if the former drug were given alone. These experiments further show definitely that the associated drop in blood pressure is not essential to the production of sleep in amytal narcosis, since the patients continued to sleep even when the blood pressure was rising under the influence of benzedrine, although the period of narcosis was shorter. Moreover, small doses of benzedrine, which almost completely destroy the ability to sleep, do not create any change in blood pressure. It would thus seem certain that sleep is not fundamentally dependent upon either a lowered or an increased blood pressure.

The striking effects on the cellular constituents of the blood are probably due to squeezing out of cells, chiefly red cells, from various storage depots. The well known constricting effect of adrenalin on the spleen is probably simulated in this instance by benzedrine. It is also likely that cells from other organs, such as the bone marrow or the lungs, are squeezed out by effects of the vasoconstrictor action of the drug and thus appear in the circulation. The absence of immature forms of either white or red cells suggests that the increase in counts is a mechanical one and not due to stimulation of the blood-forming organs.

Summary and Conclusions. Benzedrine, a sympathomimetic drug, was studied in a group of patients with mental disease, its effect on the pulse, blood pressure, spinal fluid pressure, mental state, basal metabolism, and blood cellular constituents being noted. Its actions when used in combination with acetyl-beta-methylcholin (mecholy), a parasympathetic stimulant, atropin and sodium amytal were observed.

Benzedrine has a striking and prolonged effect in raising the blood pressure, together with a less marked effect on the spinal fluid pressure. Its effects in raising the red cell and white cell counts are often great, the erythrocyte count rising 1 to 3 millions per c.mm. and the leukocyte count often being doubled or even tripled. No effects on the basal metabolic rate or blood sugar were noted.

When used with mecholy, the blood pressure lowering effect of the latter drug was at first apparent, followed by an increased blood pressure when the effects of mecholy became diminished. When used with atropin, the rise in blood pressure was often extreme. With amytal, the period of narcosis was shortened and the blood pressure lowering effect of this drug was diminished.

As brought out in these and associated studies, benzedrine has a central stimulating effect. Its effects are, in general, those of a sympathetic stimulant, the reaction being a prolonged one of several hours' duration. Its effects on the blood cellular constituents are probably due to vasoconstriction of the spleen and other reservoirs of blood cells resulting in an increased number of cells in the peripheral blood.

The effects of the combined administration of benzedrine with

mecholyt, atropin, and sodium amytal are exceedingly interesting and suggest that it may be possible to equilibrate sympathetic and parasympathetic drugs against each other, and thus obtain enhanced effects.

The central, vascular, and smooth muscle effects of benzedrine suggest its practical use in various clinical conditions. Its ability to arouse narcoleptics has already been mentioned. Its stimulating effect in psychoneuroses and in mental and fatigue states is important and is elaborated upon in an accompanying article. Because of its ability to raise and maintain arterial pressure over a period of several hours, its use in counteracting an expected fall in blood pressure, as for example in anesthesia, or in raising the blood pressure in conditions of peripheral circulatory failure, as in shock, pneumonia, etc., is suggested. It may be of value as well in the ill-defined condition known as primary or postural hypotension. Its use in diminishing increased tonus of organs made up in great part of smooth muscle—such as the gastro-intestinal tract, the ureter, and gall bladder—seems to be definitely indicated. The use of benzedrine in individuals known to have hypertension or severe vascular or cardiac disease is probably contra-indicated.

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BOOK REVIEWS AND NOTICES.

DISEASES OF THE LIVER, GALL BLADDER, DUCTS AND PANCREAS. Their Diagnosis and Treatment. By SAMUEL WEISS, M.D., F.A.C.P., Clinical Professor of Gastroenterology, New York Polyclinic Medical School and Hospital; Attending Gastroenterologist, Jewish Memorial and Beth David Hospitals, New York, etc. Chapter on Surgery by J. Prescott Grant, M.D., F.A.C.S., M.R.C.S., Professor of Surgery, New York Polyclinic Medical School and Hospital; Attending Surgeon, City Hospital; Director of Surgery, Midtown Hospital. Chapter on Roentgenology by A. Judson Quimby, M.D., F.A.C.R., Professor of Roentgenology, New York Polyclinic Medical School and Hospital; Visiting Roentgenologist, Broad Street Hospital. Pp. 1099; 358 illustrations, 6 color plates, and 21 tables. New York: Paul B. Hoeber, Inc., 1935. Price, \$10.00.

In covering his subject the author has attempted to include an enormous amount of material from the literature (over a hundred pages are devoted to references and an index of personal names). One, however, gets the impression that much of this material has been not too well assimilated and the reader finds the going rather heavy. If the author had condensed his manuscript by one-fourth and had been somewhat more critical of the balance, he would have produced a more readable and a more authoritative text. Aside from these shortcomings, the book has much to recommend it. The historical notations are interesting. The discussion of examination of liver and gall bladder, the sections on pathology and particularly the illustrations, are well done.

R. K.

THE DIAGNOSIS AND TREATMENT OF DISEASES OF THE PERIPHERAL ARTERIES. By SAUL S. SAMUELS, A.M., M.D., Chief of the Clinic for Peripheral Arterial Diseases, Fourth Division Bellevue Hospital, New York; Chief of the Department of Arterial Diseases, Stuyvesant Polyclinic Hospital, New York, etc. Pp. 260; 51 illustrations. New York: Oxford University Press, 1936. Price, \$3.50.

This monograph is first of all a plea for the conservative management of thromboangiitis obliterans, to which disease almost two-thirds of the book is devoted. The demonstration of the very frequent good results of such therapy, reflecting a large experience with Buerger's disease, give the book its chief value.

The author is equally intent in his partiality toward the intravenous hypertonic saline treatment for obliterative diseases of the peripheral vessels. Though recognizing the need for all available proven methods that promote collateral circulation, he dismisses, with evident lack of understanding, such methods as intravenous typhoid antigen injections, alternating suction and pressure, and sympathetic ganglionectomy, methods which other competent judges regard as useful. A statement frankly admitting insufficient experience with such procedures for sound judgment, or that they had failed after thorough trial in his hands, would seem more in keeping with the expressed purpose of the book.

Likewise the vasospastic disorders and their differentiation from occlusive disease, deserve more detailed consideration than they receive in this treatise intended to cover diseases of the peripheral arteries.

The book contains many sensible and extremely valuable diagnostic and therapeutic suggestions tersely stated. In this respect and in its well documented case for conservatism it is of real value to the practitioner.

L. H.

TIME OF OVULATION IN WOMEN. A Study of the Fertile Period in the Menstrual Cycle. By CARL G. HARTMAN, Department of Embryology, Carnegie Institution of Washington, John Hopkins Medical School, Baltimore, etc. Pp. 226; 72 illustrations. Baltimore: The Williams & Wilkins Company, 1936. Price, \$3.00.

THIS small volume gives a thorough analysis of the present knowledge of human ovulation with particular reference to the Oginio-Knauss theory of a "safe" period. The clear and concise explanations will be easily grasped by the more intelligent laity, although the book is not primarily offered to them. The text discusses the physiology of the germ cells, the sex cycle, the menstrual cycle and its variations. The time of ovulation is discussed especially in its physiologic and hormonal relationships.

Ovulation as observed in the Carnegie Institute monkey colony is compared with ovulation in the human. He brings out the practical application of the present understanding of ovulation in the human to the correction of apparent sterility. The large number of well executed graphs should lend greatly to a quick and clear understanding of the text by a lay reader. For physicians this very instructive review will provide a means for easy explanation of the biologic mystery of conception to patients.

P. W.

FOUNDATIONS OF SHORT WAVE THERAPY. Physics-Technics-Indications. Physics and Technics by WOLFGANG HOLZER, DR. MED., Assistant in the Physiologic Institute of the University of Vienna; Medical Applications by EUGEN WEISSENBERG, DR. MED.; Medical Superintendent of the Short Wave Section of the University Clinic for Nervous and Mental Diseases in Vienna. Translated by JUSTINA WILSON, F.R.C.P. (EDIN.), D.M.R.E. (CANTAB.), and CHARLES M. DOWSE, B.Sc. ENG. (LOND.), A.M.I.E.E. Pp. 228; 53 illustrations and 10 tables. London: Hutchinson & Co., Ltd., 1936. Price, 12/6.

THE technical section of the book illustrates an attempt at treating a somewhat advanced subject in an elementary fashion. This led to partial inaccuracies. The terminology was not always good but this may be a difficulty in translation.

In regard to the mechanism of action, it is the feeling of some authors that it is unlikely that there is any specific action of short wave therapy on the nervous system but that similar results might be obtained by an external application of heat.

The portion by Dr. Weissenberg on medical applications is a comprehensive survey of the application of short wave therapy to a great variety of medical and surgical conditions. Both the literature and the author's personal experience are drawn upon in illustrating results.

An introductory chapter describes the biologic action of the waves as due to electrical stimulation of the nervous system with local heat playing but a small rôle.

Both according to theory and the author's experience, lesions most suitable for this form of therapy may be placed in two groups. In the group of superficial inflammations, the local heat and vasodilation produced by the electrical field abort early cases and hastens localization in late. In the organic diseases of the nervous system, particularly diseases of the peripheral nerves, repeated exposure to very weak electrical fields is reported to produce rapid relief of symptoms.

In the field of internal medicine and surgery the cases reported are too few to permit judgment on the merits of this form of therapy. The authors are enthusiastic. It seems probable that short wave therapy will become a valuable adjunct in the symptomatic treatment of systemic disease in

selected cases. That it can lead to a permanent cure throughout the wide range of diseases in which the authors describe its use is extremely doubtful.

The medical section of the book is concise, covering in a page or two each the results of treatment in the various conditions in which it was employed. An attempt is made to state facts without prejudice. From the medical standpoint, this book is of value to those interested in this relatively new field. It provides a base-line upon which future knowledge may be built.

E. P.

THE SPECIFICITY OF SEROLOGICAL REACTIONS. By KARL LANDSTEINER, M.D., The Rockefeller Institute for Medical Research, New York. Pp. 178. Springfield, Ill.: Charles C Thomas, 1936. Price, \$4.00.

THOSE interested in the chemical aspects of immunity will welcome this revised edition of Dr. Landsteiner's book, originally published in German, and now re-written for American publication. Although it is based on the extensive investigations of the author and his co-workers, it also represents an exhaustive cross-section of the literature of immunochemistry; and the value of this bibliography is enhanced by its organization into the body of the text.

The book begins with a discussion of the specificity of naturally occurring protein and cell antigens, and a chapter on the specificity of antibodies. There follows a consideration of artificially conjugated antigens, and the reactivity of the corresponding antibodies with simple chemical compounds. The last chapter deals with the recent work on the serologic reactivity of specific cell carbohydrates and lipoids.

The present status of our knowledge of specificity is accurately reflected by the stress placed on the presentation of the actual experimental data rather than their premature interpretation, and by the fact also that in a book of this size, it was found necessary to devote only 14 pages to antibodies.

H. E.

PEDIATRIC NURSING. By JOHN ZAHORSKY, M.B., M.D., F.A.C.P., Professor of Pediatrics and Director of the Department of Pediatrics, St. Louis University School of Medicine; Pediatrician-in-Chief to the St. Mary's Group of Hospitals, etc., assisted by BERYL E. HAMILTON, R.N., Graduate of St. Luke's Hospital, St. Louis. Pp. 568; 144 illustrations and 7 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, \$3.00.

THIS book should be heartily welcomed by pediatric instructors as meeting the needs produced by the rapid changes in this vast field of caring for the sick child and for the proper development of the baby and the well child. The subject material is clearly and simply outlined. Each chapter deals directly with practical points and sound theories as a guide in rendering understandable nursing care to the sick individual. An interesting order of the development from the psychological aspect avoiding the difficult fads of recent years is noted. The book contains common sense indications for guidance of the baby into normal health and natural habits. The nursing points are concise and well emphasized in their descriptive manner.

The illustrations of the technical procedures, of which so many books have too few, are a valuable asset. They serve as a reminder of the demonstrations given to the students and portray a clear picture of the technique.

The chapters on "Home and the Family" and "Child Psychology" bring a refreshing appeal to the reasonable sensible approach of the parents and the nurse in managing the child. A wide scope of information is given to enlighten those who devote their time in caring for babies in an intelligent wholesome humane way.

B. L.

1^{ère}: SEMAINE MÉDICALE INTERNATIONALE EN SUISSE, MONTREUX, 9-14 SEPTEMBRE, 1935. Organisée par le Journal Suisse de Médecine. Sous le patronage du Haut Conseil Fédéral de la Confédération Suisse. Pp. 477; illustrated. Bale: Benno Schwabe & Cie, 1936. Price, Sw. Fr. 20.

THIS report of the first Swiss International Medical Week plunges so abruptly *in medias res* that one can find nothing about the nature of the gathering except that it was organized by the Swiss Journal of Medicine, under the patronage of the Federal Council of Switzerland and was attended by some 250 doctors from several countries. The 29 addresses, many by well-known European authorities, are grouped under the general headings of General Therapy, Vitamines and Hormones (included in this section is Sigerist's "The Present Unrest in the Medical World!"), Internal Medicine, Pediatrics and Nutrition, Cancer and Radiation Therapy, and Actual Problems (!). The various presentations, as might be expected, show a considerable variation of excellence.

E. K.

THE BABY AND GROWING CHILD. Feeding and Health Care for Physicians, Mothers and Nurses. By LOUIS FISCHER, M.D., Consulting Physician to the Willard Parker Hospital, New York City, and St. Vincent's Hospital, Montclair, N. J., etc. Pp. 260; many illustrations, some in colors. New York: Funk & Wagnalls Company, 1936. Price, \$1.50.

In the opinion of the Reviewer, this is another volume on the care of children which goes too far in what it attempts. It would seem reasonable to suppose that a certain amount of standard and fundamental information should be placed at the disposal of young mothers. In the opinion of the Reviewer, and this opinion is shared by many other pediatricians, this body of fundamental facts can be condensed into a very short volume. It is not good judgment to encourage the diagnosis and treatment of disease or disorders of nutrition by the laity.

E. T., Jr.

PROTOPLASM. By WILLIAM SEIFRIZ, PH.D., Professor of Botany, University of Pennsylvania, Philadelphia. Pp. 584; 179 illustrations. New York: McGraw-Hill Book Company, Inc., 1936. Price, \$6.00.

THE subject of this book is "living matter in its simplest form." Though the description of Dujardin, the discoverer of protoplasm (1935), is still "as accurate as any that can be given," and though this presentation is for students in biology and medicine in form "as nontechnical as is consistent with accuracy and completeness (!)" yet a wide range is covered in a way that demands careful study by colleagues as well as students. Exemplifying the opening quotation from Descartes on the interdependence of science, the 27 chapters proceed from such technical fields as micrurgy and tissue culture to 9 chapters on the biophysics of colloids, osmosis, elasticity and so on; 2 on electrophysiology; 5 on the biochemistry of salts, carbohydrates, fats, proteins and regulatory substances; concluding with one on "the origin of living matter." This predominantly physical approach is in line with the *Zeitgeist*, as is the avoidance of "severely adverse or destructive criticism and finality in statement, for both are out of place in science, especially today, when change and doubt are the very spirit of scientific thought." Lacking the special knowledge that the author so obviously possesses, the Reviewer refrains from any attempt to criticize the subject matter; he has a strong impression that this is an accurate presentation of an important subject in an able, up-to-date manner.

E. K.

NEW BOOKS.

- A Manual of Practical Obstetrics.* By O'DONEL BROWNE, M.B., B.Ch., B.A.O., F.R.C.P.I., L.M. (Rotunda Hospital), M.C.O.G., Assistant Gynaecologist, Sir Patrick Dun's Hospital, Dublin; Assistant to the Professor of Midwifery, Trinity College, Dublin. Pp. 363; 236 illustrations and 10 plates, some in color. Baltimore: William Wood & Co., 1936. Price, \$6.50.
- The Thyroid.* Surgery, Syndromes, Treatment. By E. P. SLOAN, M.D. Edited by Members of the Sloan Clinic: GUY A. SLOAN, M.D.; H. P. SLOAN, M.D.; FRANK DENEEN, M.D.; H. W. WELLMERLING, M.D.; O. H. BALL, M.D., and with a Foreword by WILLIAM SEAMAN BAINBRIDGE, M.D. Pp. 475; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, \$10.00.
- The Toxæmias of Pregnancy.* By DAME LOUISE McILROY, D.B.E., LL.D., M.D., D.Sc. (GLASG.), D. Sc. (LOND.), D. Sc., HON. (BELFAST), F.C.O.G., M.R.C.P., Consulting Obstetrician and Gynaecological Surgeon, Royal Free Hospital; Surgeon, Marie Curie Hospital, etc. Pp. 355; 19 illustrations. Baltimore: William Wood & Co., 1936. Price, \$5.00.
- Diätetik.* Die Ernährung des Gesunden und des Kranken. By Privatdozent DR. WILHELM HEUPE, Oberarzt an der medizinischen Universitäts-Poliklinik, Frankfurt A. M. Band XX of Medizinische Praxis, Sammlung für ärztliche Fortbildung. Pp. 192. Dresden: Theodor Steinkopff, 1936. Price: Paper, Rm. 9.50; bound, Rm. 10.80.
- Tissue Immunity.* By REUBEN L. KAHN, M.S., D.Sc., University of Michigan, Ann Arbor. Pp. 707; illustrated. Springfield, Ill.; Charles C Thomas, 1936. Price, \$7.50.

NEW EDITIONS.

- The Operations of Surgery.* Vol. 1. The Upper Extremity, The Head and Neck, The Thorax, The Lower Extremity, The Vertebral Column. By R. P. ROWLANDS, M.S. (LOND.), F.R.C.S. (ENG.), Late Surgeon to Guy's Hospital; Late Lecturer on Surgery to the Medical School, and PHILIP TURNER, B.Sc., M.S. (LOND.), F.R.C.S. (ENG.), Consulting Surgeon to Guy's Hospital; Formerly Lecturer on Surgery and Teacher of Operative Surgery to the Medical School. Pp. 1043; 435 illustrations (38 in color). Eighth edition. Baltimore: William Wood & Co., 1936. Price, \$10.00.
- An Index of Treatment.* By various writers. Edited by ROBERT HUTCHINSON, M.D., LL.D., F.R.C.P., Consulting Physician, London Hospital, and Hospital for Sick Children, Great Ormond Street. Pp. 1020; 147 illustrations. Eleventh edition, revised. Baltimore: William Wood & Co., 1936. Price, \$12.00.
- Blutung und Fluor.* By PROF. DR. HANS RUNGE, Direktor der Universitäts-Frauenklinik Heidelberg. Band IX of Medizinische Praxis. Sammlung für ärztliche Fortbildung. Pp. 117; 18 illustrations. Second enlarged edition. Dresden: Theodor Steinkopff, 1936. Price, paper, Rm. 7; bound, Rm. 8.
- A Textbook of Pathology.* By W. G. MACCALLUM, Professor of Pathology and Bacteriology, The Johns Hopkins University, Baltimore. Pp. 1277; 697 illustrations. Sixth edition, entirely reset. Philadelphia: W. B. Saunders Company, 1936. Price, \$10.00.

PROGRESS OF MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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MALIGNANT TUMORS OF THE UTERINE BODY.

IN the present review, as the title indicates, we shall exclude the more common carcinoma of the cervix and confine ourselves to several malignant neoplasms which involve the fundus of the uterus, the most common of which is adenocarcinoma. In order to obtain anything like a satisfactory result in dealing with uterine cancer, it is necessary to make an early diagnosis. Of all symptoms which should make us suspicious of this disease, the most important is postmenopausal bleeding, which, however, does not always indicate the presence of cancer. This subject has been studied in a series of 315 cases of postmenopausal hemorrhage by Schulze,¹ who found that in 215 cases, or more than two-thirds of the total number, the bleeding was due to a malignant tumor of the genital tract and of these the very great majority were uterine tumors. Carcinoma of the cervix was present in 153 patients, in 14 of which the carcinoma had developed in the cervical stump following supravaginal hysterectomy. The histologic diagnosis of adenocarcinoma of the stump appearing rather soon after supravaginal hysterectomy aroused the suspicion in 3 of these cases that the tumor might have arisen from a fundal adenocarcinoma overlooked at the primary operation. Fifty-one women in the series had fundal adenocarcinoma, 2 had sarcoma and 1 had a chorioepithelioma; 3 women had vaginal carcinoma, 2 had urethral carcinoma and 1 had a vulvar cancer. Among the ovarian tumors associated with postmenopausal hemorrhage were 2 ovarian cancers and 2 granulosa cell tumors. Benign tumors causing bleeding are relatively infrequent in older women. There were only 5 myomata in the series but mucous polypi, both of the fundus and of the cervix are comparatively common and are usually an obvious cause of hemorrhage. Other more or less common causes of postmenopausal bleeding are: that due to trauma to a prolapsed uterus, ill fitting pessaries, senile vaginitis, trichomonas infestation, urethral caruncle and endocervicitis. This study shows that by no means all postmenopausal bleeding is due to fundal cancer, but it also shows that this disease is common enough in patients who present this symptom, that in the absence of any obvious

explanation of the bleeding, cancer must be considered as probable until it is definitely excluded.

A study of case histories of patients with fundal cancer at The Mayo Clinic has been made by Judd, Phillips and Waldron.² They found that the patients usually come for consultation because of a troublesome vaginal discharge or because of some irregularity in the menstrual cycle, and that ordinarily pain is not a feature of the complaint until later in the course of the disease. A persistent increase in the menstrual flow, or spotting between the periods after the age of 35 years should be carefully investigated, particularly if it occurs after the menopause. They found that between 60 and 65% of carcinomas of the uterine body are observed after the menopause. Fortunately, carcinoma of the body of the uterus has a tendency to be confined to the endometrium and does not invade the muscular wall of the uterus or extend to the peritoneum for a considerable time. This is partially explained by the fact that the lesions are usually not of the active type as classified according to Broders' index of malignancy, being usually of Grade 1 or 2. Extension to the lymph nodes is uncommon because the uterine muscle limits the growth and forms a barrier to the lymph channels so that there is a satisfactory response to treatment in many cases in spite of the duration and local extent of the disease.

Some interesting biometric studies on endometrial cells have been made by McCormack,³ who measures the size of the nucleus and nucleolus of cells of the uterine glands in various pathologic conditions, to determine the relation that exists between them, especially in benign as contrasted with malignant conditions. Forty-eight specimens of endometrium were studied; these consisted of 34 specimens of hypertrophied endometrium, 4 of adenomyoma, 6 of polypoid endometrium, and 4 of adenocarcinoma. Twenty cells in each of the 48 specimens were studied. In malignant tissue, sections of the nuclei average 64.9 square microns in area, while in benign tissue, sections of the nuclei average 51.7 square microns. In malignant tissue, sections of the nucleoli average 3.9 square microns in area while in benign tissue they average only 1.4 square microns. In malignant cells the ratio in size of nucleolus to nucleus is 1:16.6 while in benign cells this ratio is 1:36.9. This study shows clearly that the important biometric differences between malignant and benign cells are: (1) the larger nucleus and nucleolus in the malignant cell, and (2) the smaller ratio that exists between the size of the nucleolus and nucleus in the malignant cell.

While it is usually assumed that all cancers of the fundus of the uterus are adenocarcinomas, it should be remembered that in exceptional instances the growth may be a *squamous cell carcinoma*. Gellhorn⁴ has reported 2 personal observations of this type to be added to the very scanty international literature on the subject. Of course, squamous cell cancer cannot develop directly from the cylindrical epithelium of the endometrium. There must first occur as a connecting link a change from the cylindrical to the pavement epithelium. This metaplasia may be either the result of certain conditions acquired during the lifetime of the individual or it may be the expression of a faulty embryonic development.

Surgical Treatment. In order to determine whether operation or irradiation gives the better results in fundal cancer, Nordineyer⁵ analyzes the results from the gynecologic clinic at Goettingen and compares

them with the world literature on the subject. At his clinic, from 1926 to 1930, there were 78 cases of fundal cancer, all microscopically proven. Of these, 62 were operable and 16 inoperable. The absolute cure rate, (that is, the percentage of cures to the total number seen) was 46.1%. The relative healing of the operable cases was 58%, while there were no cures in the inoperable cases. Of the operable cases 34 were treated by surgery and 28 by irradiation. Of the 34 operated upon, 24 were cured (70.6%), while of the 28 treated by irradiation, 12 were cured (42.9%). The primary mortality of operation was *nil* while irradiation gave a primary mortality of 9.1%. In the world literature which he collected, surgery gave a cure rate of 56.8% against a rate of 50.5% for irradiation.

Reporting from Stoeckel's clinic in Berlin, Volbracht⁶ states that in the period from 1926 to 1930 they treated 112 patients, of which 70 were operated upon with a mortality of 7.1% with a recurrence rate of 25.7% and a 5-year curability of 67.1%. Of the 42 who were treated by irradiation alone there was a primary mortality of 2.4% recurrence in 50% and a 5-year cure in 47.6%. As a result of this comparison he believes that operation is the treatment of choice, especially since the rate of operability is high. Of course radium irradiation must be used in the inoperable cases and in those in whom surgery is contraindicated because of associated serious systemic disease.

Beattie⁷ calls attention to the fact that several histologic types of adenocarcinoma may be found in any one specimen so that it is impossible, in all cases, to diagnose the histologic nature of the main mass of a carcinoma from curettings alone. For this reason he believes that the prognosis cannot always be based upon the histologic report, as so many investigators, particularly in this country, have stated in recent years. As to treatment, his series has shown to his satisfaction that surgery is the method of choice, since surgery with or without supplementary irradiation gave 58% of 5-year cures as opposed to 18% of 5-year cures in the cases receiving irradiation alone.

In reporting a series of 56 patients which they treated, Newell and Crossen⁸ state that in comparing the results of different methods of treatment for any grade of corpus carcinoma, the comparison should be made with cases of the same approximate extent, that is, early cases to early cases and late cases to late cases. Otherwise there may be erroneous conclusions as to the efficacy of the different methods of treatment. This point is illustrated by their series in which death resulted in nearly all patients receiving only irradiation; which would seem to indicate that irradiation has very little curative effect. But when the extent of the disease is considered, we find that practically all cases presenting reasonable hope of cure were subjected to operation, irradiation alone being limited to the hopeless cases. They feel at present that operation plus irradiation is the safest plan of treatment. If the patient is a good operative risk, hysterectomy is performed and is supplemented by irradiation to devitalize any cancer cells which may be beyond the structures removed. This may be given before or after the operation or both, and may be given by Roentgen ray or radium or both. In their series 20 cases were treated by operation alone with 13 cures for over 5 years, 23 were treated by operation plus irradiation with 14 cures for over 5 years, while irradiation alone gave only 2 cures in 13 cases treated.

At The Mayo Clinic, according to Judd, Phillips and Waldron,⁹

total abdominal hysterectomy with removal of both tubes and ovaries is the preferable treatment because of the tendency of carcinoma in this location to be of low grade and to remain localized.

Removal of the tubes and ovaries is essential, for it precludes the possibility of development of secondary growths from malignant cells that may have migrated to these tissues. The immediate mortality rate is lower following this operation than it is after hysterectomy of the Wertheim type. Such satisfactory results have been obtained by them that they have been encouraged to extend the operation to some cases in which widespread involvement precluded anything more than temporary relief. In many of these cases it has controlled the process for a much longer period than could reasonably have been anticipated. Late in the course of the disease the bladder, rectum and vagina may be involved in a solid carcinomatous mass. In these cases and in those in which the risk of surgical procedure is definitely out of proportion to the benefit to be obtained, the use of radium may have some palliative effect.

Irradiation Therapy. Based upon the results obtained in his large experience at the Memorial Hospital in New York, Healy^{9, 10, 11} has become a strong advocate of irradiation therapy in fundal cancer. He states that for a long time it has been generally assumed that, since carcinoma of the corpus is a glandular variety of cancer, it is radiation resistant, and irradiation therapy could not be used to advantage to control tumor growth. However, irradiation has been used in patients who declined operation or were poor risks for major surgery and it has been noted that such patients were often benefited and at times apparently cured. Moreover, it was recognized that a great many patients in whom hysterectomy had been done did not remain well but developed local recurrences or distant metastases 2 or 3 years after operation and ultimately died of cancer. He divides corpus cancers into four histologic groups:

1. Papillary adenoma malignum. The growth is entirely papillary and may not be superficial but as a rule does not tend to invade the myometrium. It resembles adenomatoid endometritis and the cells show very little change from the normal.

2. Adenoma malignum. The microscopic picture is characterized by large or giant glands, often greatly elongated, lined by several layers of cuboidal and cylindrical cells. The stroma is greatly reduced and the enlarged glands adjoin each other, often in groups of 3 or 4 surrounded by strands of stroma. The nuclei of the gland cells are large and hyperchromatic and stain deeply. Any tendency on the part of the cells to break through into the stroma and to form solid masses takes the tumor out of this group and places it in the next one.

3. Adenocarcinoma. Histologically the cases in this group are characterized by greater malignancy. The cells are more atypical and there is more evidence of anaplasia than in the preceding groups and the tumor while still retaining its glandular arrangement, nevertheless infiltrates the stroma and forms solid masses of tumor cells. It is this evidence of infiltration which distinguishes this group from the preceding one.

4. Cellular (anaplastic) adenocarcinoma. Cases in this group are characterized histologically by diffuse growth of small round cells and polyhedral cells often entirely lacking in glandular arrangement. The

cells may be closely packed together, stroma scanty, mitotic figures numerous and marked evidence of anaplasia is seen.

Healy observes that 100% of all Group 1 patients and 87.5% of Group 2 patients are alive, regardless of the plan of treatment followed. This would seem to indicate that the disease in these histologic types remains localized in the uterus for a long time and if the risk of hysterectomy is not too great, a cure may be obtained by this procedure. On the other hand, when operation is contraindicated, irradiation may be carried out to advantage. He believes it is highly significant that the patients in whom irradiation was used in full dosage, either alone or some weeks before hysterectomy have remained free from recurrent or metastatic disease and have lived longer than those patients treated by hysterectomy before irradiation or by hysterectomy alone. In view of the marked difference in end results in the two major histologic types represented by the adenoma malignum type and the adenocarcinoma type and therefore, the prognostic value of knowing as soon as possible the histologic type in which the particular case falls, it would seem highly desirable to obtain tissue from within the uterus for microscopic study before even curettage is done. If this is not possible, a quick report from either frozen section at the time of curettage or in 4 or 5 hours would be helpful in planning treatment. In adenocarcinoma, even if the patient is in condition for hysterectomy, he believes that it is best to institute a full dosage of intrauterine irradiation supplemented by deep Roentgen ray therapy previous to hysterectomy. Also in order to permit the full effect of irradiation to be obtained the operation should be delayed from 4 to 6 weeks following irradiation. Post-operative irradiation with radium applied in capsules throughout the length of the vaginal tube and a Roentgen ray cycle should be utilized as an additional precautionary measure 8 to 12 weeks after hysterectomy in cases of adenocarcinoma. In his experience 39% of the patients with adenocarcinoma die within 3 years, whereas in the adenoma malignum varieties only 7% die within the first 4 years. Two interesting observations have been made on this combined method of treatment; first, the hysterectomy has not been made more difficult because of the pre-operative irradiation and, second, very little viable cancer and in more than half the cases no cancer at all could be found in the uterus on microscopic examination after its removal. In his series of 134 cases there has been no operative mortality. In the cases treated by irradiation alone, it is desirable to check the result by an exploratory curettage about 12 to 16 weeks later and if cancer is found further irradiation therapy is indicated, or if possible the uterus should be removed.

At the Woman's Hospital in New York, Ward¹² found that carcinoma of the fundus occurs in about 10% of the cases of uterine cancer, and since 1919 there have been 134 such cases in that hospital. Of the 92 patients who have been treated, 61 received irradiation alone, 25 were treated by radium and hysterectomy, and 6 received operation alone. As this type of disease is more frequent in the later decades of life, many patients are poor operative risks on account of old age, obesity, cardiovascular disease, deficient renal function or diabetes. These complications were present in more than 50% of his cases, so that radiotherapy alone had to be relied upon.

Voltz¹³ states that from 1913 to 1928 in the irradiation clinic of Docderlein in Munich, there were 138 cases of fundal cancer treated by

irradiation, of whom 56 (40.6%) were alive and free from disease 5 years later.

Sampson¹⁴ is of the opinion that radium is of value in those cases in which it can be brought into intimate contact with the growth, but as a result of his laboratory studies he has found that in many instances it is a matter of chance as to whether the radium gets into such intimate contact. He has made skiagrams of uteri removed at operation, with and without carcinoma of the body, in which capsules have been placed just as would be done in the radium treatment. He found that the radium may not get into intimate contact with the cancer due to faulty technique in placing the capsules, large uterine cavities, cavities of the Y type with carcinoma in one or both cornua, intramural myomas or polyps which deflect the capsules or shield part of the growth from the radium and bulky carcinomas which distend the uterine cavity. Unfortunately the presence of such conditions can be determined with certainty only after the organ has been removed and even then there may be metastases to other organs which cannot be detected. However, in spite of the uncertainties of the intrauterine application of radium, he believes that it is of the greatest value in many instances. We are much better able to judge the condition of the patient as a surgical risk than we can foretell if all of the growth can be reached by radium. Because of the inability to make an accurate pretreatment diagnosis of the exact situation and extent of the growth and the fact that all of the carcinoma may sometimes be removed where radium would fail, he believes that the removal of the entire uterus, tubes and ovaries is indicated in patients who are good surgical risks. Radium is indicated in hazardous surgical risks, especially when the uterus is small and the adnexa are not enlarged and also in evident irremovable carcinomas.

Chorioepithelioma. Although in discussions concerning malignancy of the uterus the type known as chorioepithelioma is always considered, in reality it is quite a rare disease and few clinics have an opportunity of observing more than a very occasional case. In discussing this subject, Black¹⁵ presents the important points to be remembered in connection with its diagnosis and treatment. He stated that a uterine hemorrhage or a blood tinged discharge following pregnancy (especially a hydatidiform mole) with a positive Asehheim-Zondek test, should arouse suspicion of a chorioepithelioma. It should be remembered that while almost half of the cases follow moles, only about 1% of moles are followed by chorioepitheliomas: therefore, a hysterectomy or large doses of radium are not justifiable in young women with moles. In the cases which have been definitely diagnosed chorioepithelioma from the histologic examination of the curettings, especially in the presence of a typical clinical history, a panhysterectomy should be performed and irradiation treatment instituted. As embryonic cells are very sensitive to radium rays, radium is a good prophylactic and curative agent in selected cases. Repeated Asehheim-Zondek tests following moles and especially hysterectomy for chorioepithelioma are of paramount prognostic importance, since the pregnancy reaction in mice is twelve times stronger in a mole and chorioepithelioma than in a 2-months' gestation, so that the persistence of the reaction after labor or abortion should be regarded with suspicion. On the other hand, if such patients present a

negative reaction to the test, one may feel reasonably assured of no further trouble.

Mathieu and Palmer¹⁶ feel that in the light of our present knowledge, chorioepithelioma can be definitely diagnosed shortly after its inception. They believe that every patient who passes a mole should have her urine examined for anterior pituitary-like hormone by the Friedman test monthly for a year at least. In this way a developing chorioepithelioma might be diagnosed and removed before symptoms appear or before metastases develop. They report 2 cases in which the diagnosis was made early in this way, the patients operated upon and cured. The first case was diagnosed 2 months and 4 days, the second 3 months and 4 days after the passage of a mole. They believe that their first case is unique. Following the curettage for the removal of the hydatid material the patient was absolutely free from symptoms. There was no more bleeding, her blood count increased, the uterus and pelvic contents were normal to palpation, she was in good health, free from complaints and had gained weight. There was no cough nor any sign of lung involvement. The sedimentation rate remained slightly increased and the Friedman test was persistently positive. In all the other cases reported there was bleeding, signs of metastases, enlargement of the uterus or some other signs of chorioepithelioma. The question of removal of the ovaries in conjunction with hysterectomy for this disease will bear discussion. In other forms of malignancy there will be less danger of recurrence if a complete operation is done. However, these authors believe that in cases of chorioepithelioma diagnosed early, one need not remove the ovaries. In their first case only a supravaginal hysterectomy was done and there was no evidence of recurrence. In the second case a complete hysterectomy was done because of severe lacerations of the cervix, and the right ovary was removed only because it was adherent.

Leventhal and Saphir¹⁷ state that prior to the utilization of the Aschheim-Zondek test most cases of chorioepithelioma were not diagnosed until a uterine mass was palpable, until a curettage brought forth characteristic tissue or until metastases in the lungs or vagina appeared. Often a mass was not palpated until metastases had appeared. Curettage as a diagnostic method not only is uncertain because of the possible location of the tumor at a distance from the endometrium but is dangerous, because the site of a friable growth may be perforated. The use of the Aschheim-Zondek test following a mole obviates the necessity of a curettage and its attendant dangers and is a diagnostic method by which very early chorioepithelioma may be revealed, even before a tumor is palpable or hemorrhage occurs. In the quantitative hormone test an additional method becomes available. In normal pregnancy the concentration of anterior pituitary-like substance in the urine begins to diminish after the sixth or eighth week. In a hydatidiform mole the concentration increases progressively and rapidly. In the absence of clinical manifestations, an amount of gonadotropic substance in the urine in excess of 20,000 mouse units per liter indicates an early chorioepithelioma. They diagnosed an early case solely on the basis of the laboratory finding of 333,000 mouse units in a patient who had expelled a mole 4½ months previously. Recurrence of the disease or metastases may be discovered by the Aschheim-Zondek reaction, and this should determine the use of radiation therapy.

Mazer and Edeiken¹⁸ caution that abnormal bleeding following a normal pregnancy or a mole should not be treated by radium because it masks the symptoms of chorioepithelioma and they also believe that it is impossible to make an early diagnosis of this tumor by means of uterine curettage. The source of the hormone responsible for the Aschheim-Zondek reaction is living chorionic epithelium which should not persist longer than 2 weeks after the termination of a normal pregnancy or 8 weeks after the expulsion of a mole. The quantity of the hormone excreted is proportional to the amount of abnormal chorionic epithelium present, hence a gradual increase in its excretion, with accompanying uterine bleeding following a pregnancy is indicative of chorioepithelioma.

An interesting case reported by Feiner¹⁹ is that of a 28-year-old woman in whom a vaginal tumor developed, possessing the histologic structure of a chorioepithelioma, 2½ years after the last demonstrable pregnancy. In view of the number of similar cases which have been reported, he believes that whereas in the vast majority of cases all fetal elements are destroyed by the maternal tissue within a comparatively short time after the termination of pregnancy, in exceptional instances fetal epithelia may remain dormant in the maternal host, either at the placental site or elsewhere for months or years and then be stimulated to malignant proliferation by some unknown agency. The fact that many of these cases have developed long after the menopause would effectually disprove the theory that in all such cases an intervening pregnancy has escaped detection.

Sarcoma. A group of 43 cases of sarcoma of the uterus has been analyzed by Kimbrough²⁰ in connection with a review of the literature dealing with the results of treatment. The incidence of sarcomatous degeneration in his series of myomas, as well as in the cases collected from the literature was 0.76%. The total 5-year salvage was 34.3% but taking only the 20 operable cases the 5-year salvage was 50%. The prognosis in sarcomatous degeneration of a myoma is three times more favorable than in primary sarcoma and likewise the salvage in younger women is more than three times as great as in women who have passed the menopause. Considering the histologic types, he found that the small round cell and polymorphous tumors are more highly malignant than the spindle cell sarcoma. As would be expected, the recurrences after operation were more than twice as frequent in those tumors which presented a large number of mitotic figures as in the tumors with relatively low counts and conversely, the 5-year salvage was almost four times as great in the low count groups as in the tumors showing more numerous mitoses. Therefore, although mitosis merely indicates rapid growth, from a clinical standpoint the number of mitotic figures is a reliable gauge of the degree of malignancy and hence is of prognostic value.

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ORIGINAL ARTICLES.

PROTAMINE INSULIN IN THE TREATMENT OF DIABETES
MELLITUS.*

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FOURTEEN years ago the extraction of insulin by Banting and Best, and its isolation in relatively pure form by Collip was reported to this Association, together with some of the physiological and clinical effects of the hormone.¹ This hormone has been successful in controlling practically all cases of diabetes mellitus. Two drawbacks to its use, however, were early recognized: the short duration of its action, and its tendency to bring about the clinical syndrome of hypoglycemia. With further purification, these two defects became more pronounced and insulin appeared to become almost explosive in its action. The more severe cases of diabetes required 4 or even 5 injections a day and, during the hours of sleep, hypoglycemia or hyperglycemia, glycosuria and ketosis might supervene. Examination of the blood throughout a 24-hour period revealed wide variations in the blood sugar levels, even under the most careful adjustment of insulin administration and diet.

* Read at the Association of American Physicians, May 6, 1936, Atlantic City, N. J.

The effects of purification of insulin have not been wholly undesirable. The number of local reactions to the injection of insulin has markedly diminished. Through increased rate of action of the insulin, the chances for recovery of the practically moribund comatose diabetic have probably increased. Likewise, a rapidly acting insulin is of considerable value in patients suffering from infections, previous to emergency operations on diabetics, and so on.

While many attempts have been made to slow up the action of insulin, none have proved practical clinically until Hagedorn² and his coworkers introduced a combination of a protamine and insulin, which they called protamine insulinate. This is administered in a suspension relatively insoluble at the pH of the body. Last January they reported the results of their clinical experience and stated: that protamine insulin would depress the blood sugar level twice as long as regular insulin; that hypoglycemic reactions were less frequent; and that they had treated severe cases of diabetes successfully with not more than two injections daily. These observations have been repeated and confirmed by Root, White, Marble and Stotz,³ by ourselves,⁴ and by Lawrence and Archer,⁵ and it now appears that protamine insulin constitutes an important advance in the treatment of diabetes.*

Adjustment of Dosage. Hagedorn recommended for routine use the administration of regular insulin before breakfast and protamine insulin before the evening meal. Regular insulin in this way would meet the heavier demands during the absorption of food, and protamine would answer the lighter, but more prolonged requirement during the postabsorptive period. Most cases can be brought under good control by this method of treatment.

During the past 6 months the Connaught Laboratories of the University of Toronto have furnished us with a compound insulin, using a protamine from a Pacific Coast salmon. This preparation appears to be somewhat slower in action than the Danish, and we have been able to control successfully a large proportion of cases, even the most severe, with a single injection of either protamine insulin or a mixture of protamine insulin and regular insulin.

Diabetes of moderate severity, requiring, for example, 20 to 40 units a day or ordinary insulin given in 2 doses, can usually be controlled by a single dose of 20 to 40 units of protamine insulin given in a single injection before breakfast. In the most severe cases, those which would require 60 to 100 units of regular insulin given in 3 or 4 injections, a single dose of 50 to 60 units will usually bring about fair control. Not only can the insulin be given in a single dose, but there is usually some actual economy in the number of units given. These single injections appear to be most effective

* Since this paper was read, Sprague, R. G., Blum, B. B., Osterberg, A. E., Kepler, E. J., and Wilder, R. M., have published an important paper on this subject. *Cf.* J. Am. Med. Assn., 106, 1701, 1936.

when given 1 hour or more before breakfast. Sometimes the action of protamine insulin administered in this way is not rapid enough to prevent hyperglycemia and glycosuria before breakfast, and a small amount of regular insulin may with advantage be given at the same time as the protamine insulin. It appears, however, that there is some variation in the rate of absorption and action of protamine insulin in different individuals and in a few cases the blood sugar will begin to rise considerably before the expiration of the 24-hour period. In these cases, a large dose of protamine insulin before breakfast (40 to 50 units) and a small dose of the same insulin (10 to 15 units) given at bedtime may be effective when the single injection has failed to control the glycosuria and hyperglycemia.

With diets high in carbohydrate, we have occasionally encountered cases which did not come under satisfactory control with these methods of treatment. It would appear in these cases that the blood sugar level was unstable or that the demand for insulin during the day was so much greater than at night that hypoglycemia or glycosuria at some part of the 24-hour period occurred. These cases were brought under control by the Hagedorn method. Possibly this method of using the regular insulin during the day and the protamine insulin at night may be the most suitable for this group.

Diets. Protamine insulin has been used in the treatment of patients on the different types of diet now in current use: 1, Those high in fat and low in carbohydrate;⁶ 2, diets low in fat and high in carbohydrate;⁷ and 3, diets where the amount of carbohydrate and fat are about equal by weight.⁸ We have continued to allow patients about one gram of protein per kilo of body weight, except in those markedly overweight, and have established the total calorie intake at a low maintenance level. In most cases the carbohydrate has been divided between the 3 meals, so that somewhat less is given at breakfast time and more is given at mid-day and evening meals. We have been able to bring these cases under good control by some division of dosage between the 2 types of insulin. On the whole, patients on diets high in fat and moderately low in carbohydrate have lent themselves more readily to treatment with the single large dose than patients on the other types of diet. Diets very high in carbohydrate and low in fat have been less suitable for this method of treatment. It is our impression that greater latitude in the amounts of certain foods eaten (meat, fat and low percentage carbohydrate foods) may be allowed to patients than when regular insulin alone is used.

Hypoglycemic Reactions. It is remarkable that large doses of this new insulin may be given without the development of hypoglycemic symptoms. For example: in a case in which 20 units of regular insulin before breakfast might bring about hypoglycemia before the lunch hour, 50 units of protamine insulin can usually be given without the symptoms of hypoglycemia or even undue lower-

ing of the blood sugar. Also, whereas even small increases in amount of ordinary insulin result in (1) a more precipitate fall of the blood sugar, (2), a greater degree of fall, and (3), no material increase in the duration of its action, a similar increase in the protamine insulin injected results in an increase in the duration of its action without increasing the rate of fall of blood sugar or the liability to hypoglycemic symptoms to any considerable extent. Possibly the slow rate of fall of the blood sugar is responsible for the fact that patients may tolerate blood sugar levels as low as .045% without consciousness of hypoglycemic symptoms.

Reactions have not been eliminated by the introduction of protamine insulin, but their occurrence has been markedly decreased. With the one injection of a large amount of protamine insulin before breakfast, the blood sugar has usually reached its minimum level sometime between midnight and 4 o'clock in the morning. At first this low level of blood sugar gave us considerable concern, but excessively severe reactions have not been encountered. Occasionally, it might appear advisable to give some 40% of the carbohydrate with the evening meal, and possibly some carbohydrate at bedtime, but so far we have not found this latter measure necessary. The fact demands some emphasis that, when a patient develops hypoglycemia as a result of protamine insulin, this reaction is likely to be more prolonged and carbohydrate should be available for a longer period of time than was necessary to control the former type of reaction. Recurrence or persistence of the reaction as new supplies of the insulin suspension dissolve in body fluids, may thus be anticipated and provided against. Orange juice and bread, rice or potato, or bread and honey, would appear to be suitable antidotes.

No local reactions have been encountered in our cases. This experience is similar to that of other investigators,² and it is in harmony with the view held that protamines are non-antigenic in nature.

Our experience with protamine insulin is limited to 50 cases, most of which have been diabetic and receiving insulin for a considerable time and are without interfering complications. Many have been recalled to hospital for the specific purpose of testing their behavior with protamine insulin. It has always been our practice to demonstrate that insulin is necessary before administering it but, in each case, a preliminary period of rechecking to redetermine the regular insulin requirement was carried out before transferring them to the protamine compound. The action of protamine insulin is slow, and, if only protamine insulin is used, glycosuria will occur for 2 or 3 days. The change is best accomplished by giving 75 to 100% of the previous dose of regular insulin as protamine insulin in a single morning dose accompanied, the first day, by about 60% of the previous dose of regular insulin divided in 2 doses, before breakfast and supper; and, on the second day, 30% of the previous dose before breakfast; and, thereafter, protamine insulin only. None of the 24-hour blood

sugar curves was obtained in less than 7 days from initiating the change they illustrate, in order that overlapping of previous treatments might be avoided. Initial treatment of diabetics with protamine insulin has been carried out in but few cases, but along the same lines, that is, using some regular insulin with the protamine compound for the first days.

Case Reports. CASE 1.—A male, aged 50, had diabetes of 1 year's duration. Standardized on a diet of protein 45 gm.; fat, 186 gm.; carbohydrate, 49 gm., with normal blood sugar and freedom from glycosuria on 20 units of insulin twice daily. Curve 1 shows the blood sugar level throughout the 24 hours on regular insulin, 20 units twice daily; while Curve 4 shows that a single dose of regular insulin is definitely ineffectual in controlling the blood sugar. Curves 2 and 3 show the effect of single doses of *Iridius* (Danish) and *Onchorhynchus* protamine insulin, respectively, given at 8 A.M. Saving in insulin, 50% (Cross-hatched area is zone of normal postabsorptive blood sugar levels).

CASE 2.—A male, aged 57, diabetic since 1927. On same diet and insulin since 1928. Tolerance remains the same over a 3-weeks' test. diet: protein, 60 gm.; fat, 200 gm.; carbohydrate, 70 gm. Insulin 18 units twice daily. Curve 1 shows an unexpectedly high postprandial hyperglycemia after breakfast, though the urine remained sugar-free, due to high threshold. Curve 2 shows that a single dose of 18 units of regular insulin completely fails to control the blood sugar. Curve 3 was obtained after treatment with single doses of 25 units of protamine insulin daily. This shows the marked hyperglycemia after breakfast. Without the hourly blood sugar curve, this treatment, as well as the treatment with regular insulin twice daily, would be regarded as satisfactory, as he remained aglycosuric. Treatment should be modified as suggested under Discussion.

CASE 3.—A female, aged 60, diabetic for 10 months. Diet: protein, 36 gm.; fat, 170 gm.; carbohydrate, 45 gm. Aglycosuric, normoglycemic for 3 months on 20 units of regular insulin twice a day. Curve 1 shows the blood sugar throughout the 24 hours on this procedure. Curve 2 shows an excessive hyperglycemia after breakfast by giving 25 units of protamine insulin immediately before breakfast. Curve 3 shows the value of moving back the dose 1 hour. Saving in insulin, 37%.

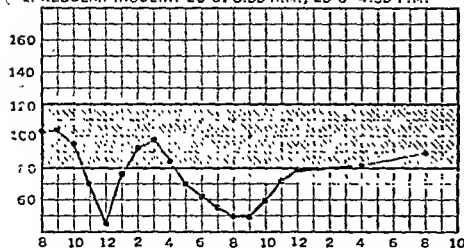
CASE 4.—A female, aged 58, diabetic since 1925. Using insulin since 1926. Felt well until a year ago when she became needle-shy and stopped the insulin though continuing with diet. Stabilized on old diet of protein, 44 gm.; fat, 160 gm.; carbohydrate, 40 gm., but now requires 3 doses of regular insulin: 30 units, 8 A.M.; 30 units, 4.30 P.M.; and 12 units at 11 P.M. Curve 1 shows the hourly blood sugar on this dosage. Substituting a single dose of 55 units of protamine insulin immediately before breakfast was hardly satisfactory (Curve 2), so a dose of 20 units of protamine insulin and 25 units of regular insulin were given together at 8 A.M. This proving satisfactory over a month's trial (Curve 3), the patient was given the two insulins in the same syringe. The curve is identical with Curve 3 save for minor variations. The patient has continued this procedure with success for 3 months. Economy of insulin 37%. Were this patient to appear for treatment now, we would move the single dose of protamine insulin alone back to 6.30 A.M., 1½ hours before breakfast.

CASE 5.—A female, aged 61, diabetic since 1928. Diet: protein, 44 gm.; fat, 140 gm.; carbohydrate, 52 gm. Stabilized on diet and insulin 3 months before. Recalled for testing and rechecked. Remained aglycosuric and normoglycemic on regular insulin: 28 units, 8 A.M.; 28 units, 4.30 P.M.; and 12 units at 11 P.M. Curve 1 shows the hourly blood sugars.

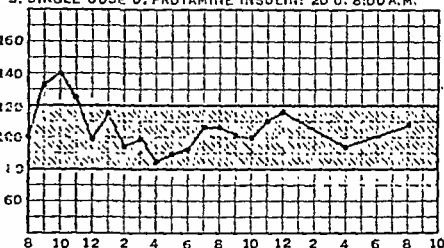
A single dose of protamine insulin at 8 A.M. was quite unsatisfactory. The Hagedorn procedure (20 units of regular insulin and 25 units of protamine insulin at 4.30 P.M.) was an improvement (Curve 3), and increasing the doses to 30 and 40 units respectively gave very satisfactory control (Curve

CASE 1

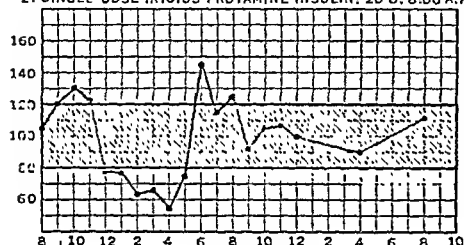
1. REGULAR INSULIN: 20 U. 8:00 A.M.; 20 U. 4:30 P.M.



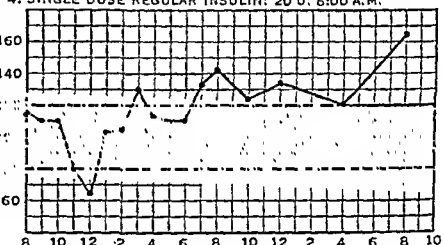
3. SINGLE DOSE OF PROTAMINE INSULIN: 20 U. 8:00 A.M.



2. SINGLE DOSE IRREGULAR PROTAMINE INSULIN: 20 U. 8:00 A.M.

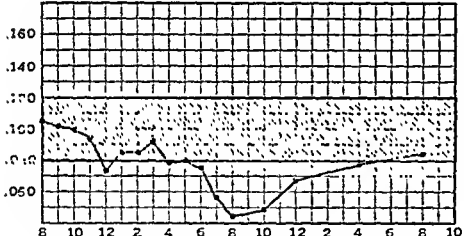


4. SINGLE DOSE REGULAR INSULIN: 20 U. 8:00 A.M.

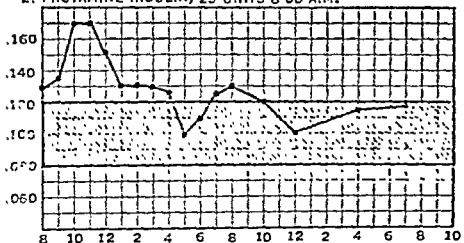


CASE 2

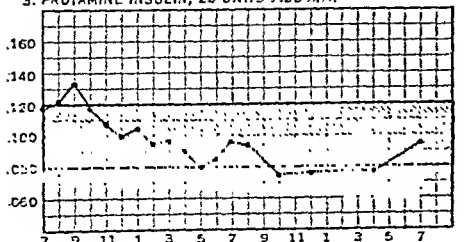
1. REGULAR INSULIN: 20 UNITS 8:00 A.M., 20 UNITS 4:30 P.M.



2. PROTAMINE INSULIN, 25 UNITS 8:00 A.M.

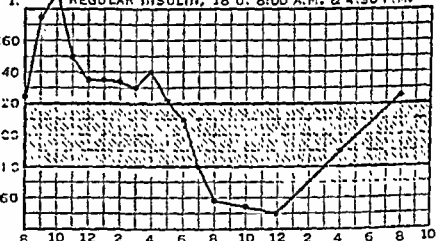


3. PROTAMINE INSULIN, 25 UNITS 7:00 A.M.

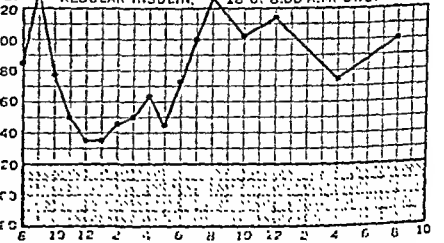


CASE 3

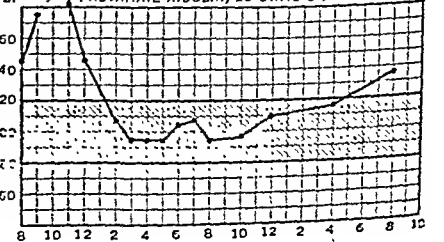
1. REGULAR INSULIN, 18 U. 8:00 A.M. & 4:30 P.M.



2. REGULAR INSULIN, 18 U. 8:00 A.M. ONLY

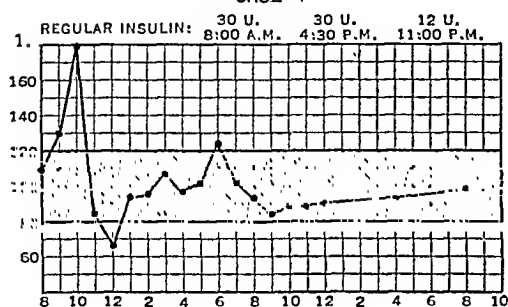


3. PROTAMINE INSULIN, 25 UNITS 8:00 A.M.

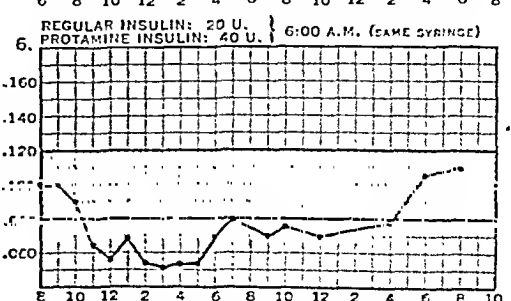
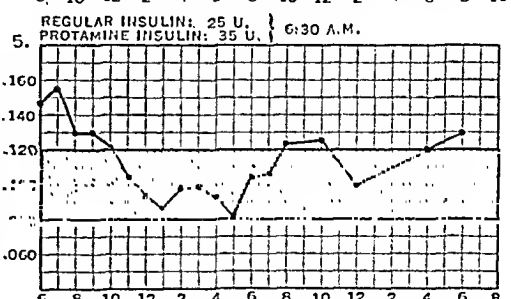
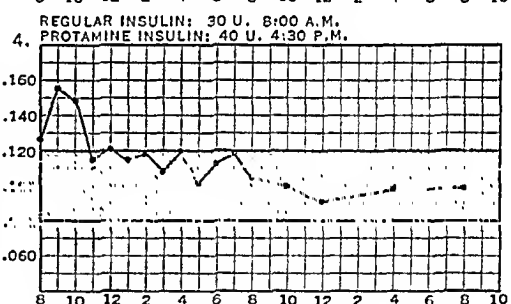
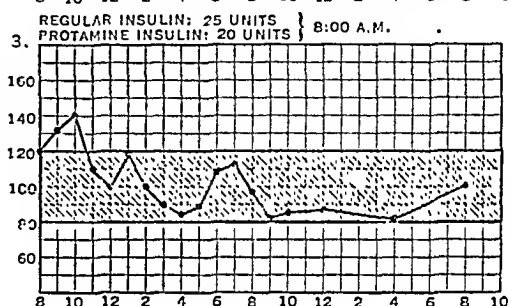
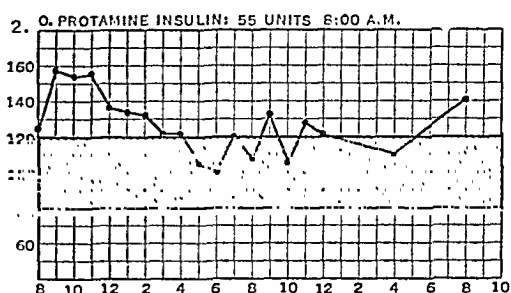
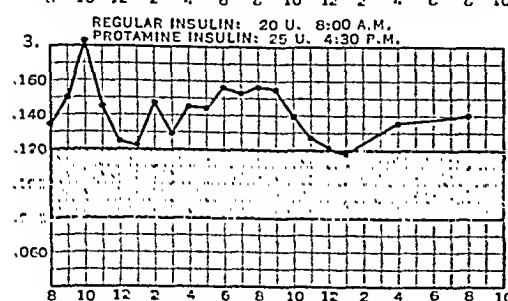
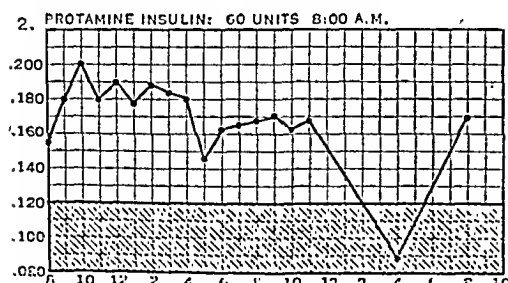
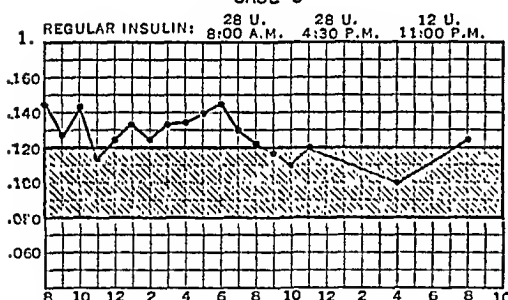


(4). The advantages of the single morning dose led us to try 25 units of regular insulin and 35 units of protamine insulin at 6.30 A.M.; breakfast at 8 A.M. (Curve 5). Alteration of this dose to regular insulin 20 units protamine insulin 40 units, given in the same syringe at 6 A.M., lowers the

CASE 4



CASE 5

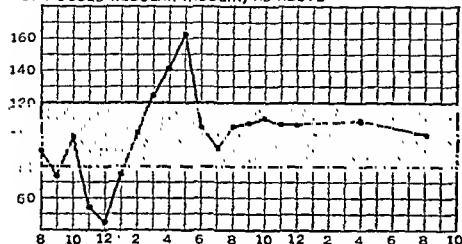


blood sugar a little too much, though the patient does not feel abnormal (Curve 6).

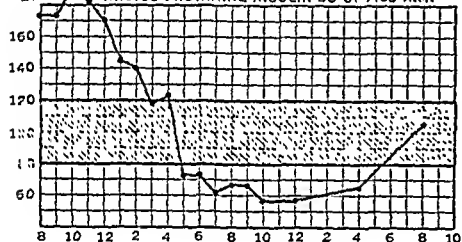
CASE 6.—A male, aged 36, diabetic since 1931. Admitted unconscious and moribund from hypoglycemia. Astonished us by recovering. Placed

CASE 6

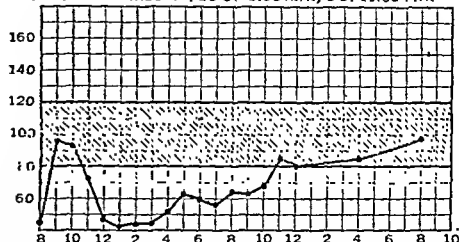
1. 4 OSES REGULAR INSULIN, AS ABOVE



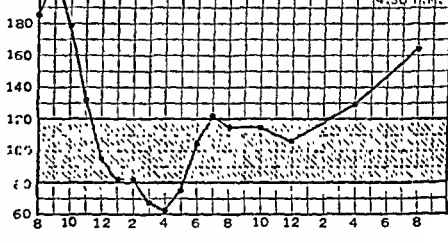
2. TRIJUS PROTAMINE INSULIN 50 U. 7:00 A.M.



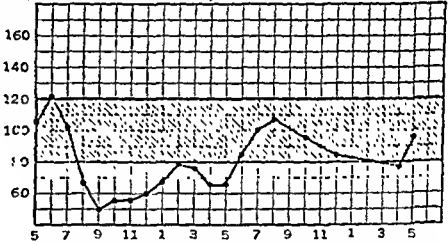
3. PROTAMINE INSULIN; 50 U. 8:00 A.M.; 5 U. 11:00 P.M.



4. REGULAR INSULIN; 30 U. 8:00 A.M.; PROT. IN. 15 U. 4:30 P.M.

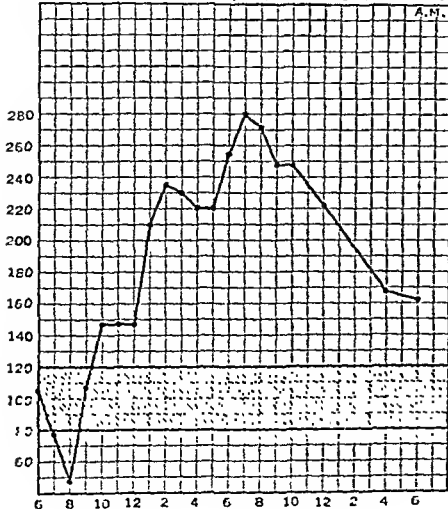


5. REGULAR INSULIN; 8 U., PROT. INSULIN 50 U. 5:30 A.M.

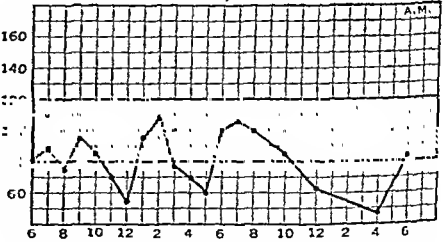


CASE 7

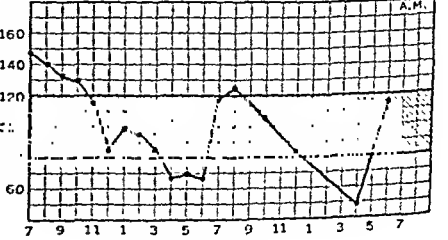
1. PROTAMINE INSULIN 60 U., REGULAR INSULIN 5 U. 6:00 A.M.



2. PROTAMINE INSULIN 60 U., REGULAR INSULIN 5 U. 7:00 A.M.



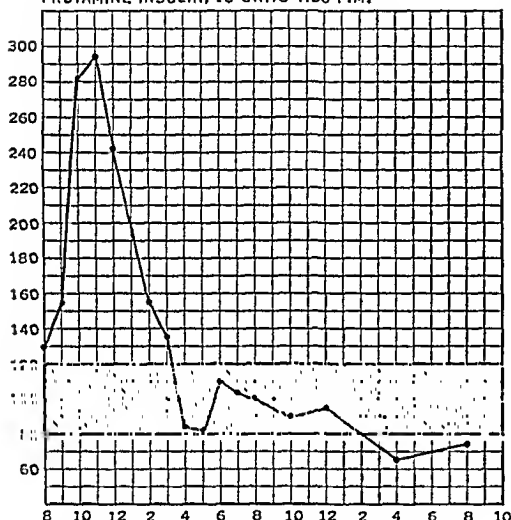
3. PROTAMINE INSULIN 50 U., REGULAR INSULIN 5 U. 7:00 A.M.



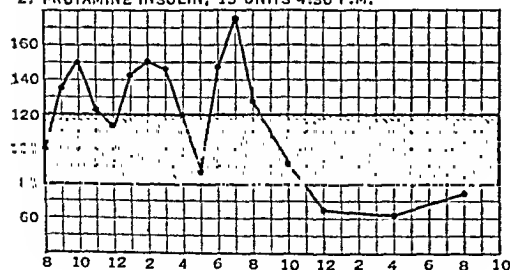
on diet: protein, 44 gm.; fat, 183 gm.; carbohydrate, 50 gm. Impossible to stabilize without using 4 doses of regular insulin daily: 4 units, 4 A.M.; 28 units, 8 A.M.; 25 units, 4.30 P.M.; 6 units, 11 P.M. Curve 1 shows the hourly blood sugars on this regimen. A single dose of protamine insulin (50 units at 7 A.M.) was unsuccessful in controlling the postprandial hyperglycemia (Curve 2). Two doses of protamine insulin (50 units and 5 units at 8 A.M. and 11 P.M. respectively) gave a more even curve which was below normal most of the day (Curve 3). Using 30 units of regular insulin at 8 A.M. and 15 units at 4.30 P.M. was probably unsatisfactory because of unsuitable dosage (Curve 4). A more satisfactory result was obtained by giving 50 units of protamine insulin and 8 units of regular insulin at 5.30 A.M. (Curve 5). As the patient was already hypoglycemic at breakfast-time, the regular insulin was reduced to 5 units, on which the patient has carried on successfully at home for the past 3 months.

CASE 8

PROTAMINE INSULIN, 35 UNITS 8:00 A.M.
PROTAMINE INSULIN, 15 UNITS 4:30 P.M.

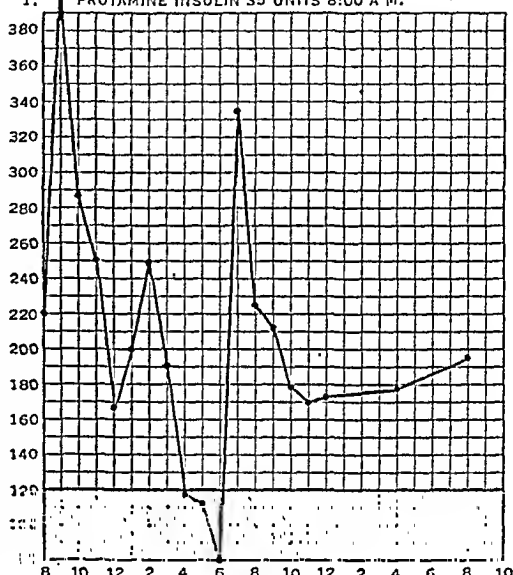


PROTAMINE INSULIN, 35 UNITS 8:00 A.M.
PROTAMINE INSULIN, 15 UNITS 4:30 P.M.

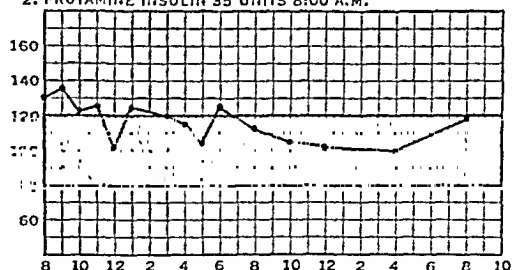


CASE 9

1. PROTAMINE INSULIN 35 UNITS 8:00 A.M.



2. PROTAMINE INSULIN 35 UNITS 8:00 A.M.



CASE 7.—A male, aged 48. In 1922, controlled successfully on diet: protein, 50 gm.; fat, 150 gm.; carbohydrate, 50 gm., with 15 units insulin twice a day. In 1930, tried on high carbohydrate diet and became unstable. In 1934, on diet of protein, 50 gm.; fat, 140 gm.; carbohydrate, 140 gm., required 5 doses of regular insulin: 5 A.M., 5 units; 8 A.M., 15 units; 12 noon, 10 units; 4.30 P.M., 10 units; 11 P.M., 5 units. In 1935, well controlled by using 5 units regular insulin at 8 A.M., and 30 units protamine insulin at 4.30 P.M. When this was substituted by 60 units of protamine insulin and 5 units of regular insulin at 6 A.M., the result was most unsatis-

factory (Curve 1). An isocaloric change to a diet of protein, 50 gm.; fat, 180 gm.; carbohydrate, 50 gm., with insulin in the same dosage at 7 A.M. improves the curve very much (Curve 2). Reduction of the protamine insulin by 10 units gives less satisfactory results both from the standpoint of the blood sugar curve and the patient's feeling of well-being (Curve 3). This patient is extremely sensitive to insulin insufficiency, reacting by fatigue, nausea and ketosis to the slightest deficiency. Since the use of protamine insulin these symptoms have disappeared.

CASE 8.—A female, aged 16, has had diabetes since 1931. On high carbohydrate diet, protein, 60 gm.; fat, 63 gm.; carbohydrate, 250 gm., it proved impossible to find a dose of regular insulin which would not produce hypoglycemia, hyperglycemia and glycosuria. On protamine insulin, 35 units, 8 A.M. and 15 units, 4.30 P.M., there is marked hyperglycemia after breakfast (Curve 1). Changing the diet to protein, 60 gm.; fat, 143 gm.; carbohydrate, 100 gm., diminishes the hyperglycemia and abolishes glycosuria (Curve 2). There is apparent here the desirability of using regular insulin to control postprandial hyperglycemia, the necessity being the greater the higher the level of carbohydrate in the diet.

CASE 9.—A female, aged 60, has had diabetes since 1926. Diet: protein, 50 gm.; fat, 50 gm.; carbohydrate, 300 gm., with a single dose of protamine insulin 35 units at 8 A.M. (Curve 1). With an isocaloric diet change to protein, 50 gm.; fat, 161 gm.; carbohydrate, 50 gm., the same dose of protamine insulin controls the hourly blood sugar curve adequately (Curve 2).

Discussion. The effect of the earliest preparations of insulin lasted as long as 24 and 27 hours. This phase was soon succeeded by another in which a better purified product gave fewer local reactions, but at the same time the action of the insulin became decidedly shorter in duration, the lowest blood sugars occurring about 4 hours after injection, and a return to the previous level occurring about 8 hours after injection. More recently, the same dose of insulin given to a normal individual depresses the blood sugar for about 3 hours in many instances. It need not necessarily be considered that the blood sugar lowering effect of an insulin represents accurately the metabolic activity of the insulin, but other facts appear to point in the same direction. Coincident with the shorter period of action on the blood sugar, it has become necessary, in a much larger percentage of cases, to resort to an increased number of doses of insulin per day, in order to maintain the patient aglycosuric. Likewise, the tendency to develop ketosis in such cases, and rapid loss of the feeling of well-being after the administration of the insulin stands in contrast to the effects of the earlier insulin preparations. Often these patients have been confused with an entirely different group, those who, through marked diminution in endogenous insulin production, have become the so-called "unstable cases," or even the "complete diabetics." The number of these cases really remains quite small, but the number of cases requiring 3 or more doses of regular insulin to maintain them in good health has risen to some 40% of the total number of cases requiring insulin. The psychological, as well as the physical advantage of being able to treat these patients with 1, or at most 2, doses of insulin cannot be

overestimated. For those patients also, who require but 2 doses of regular insulin daily, there is a very considerable convenience in being able to reduce the number of doses to 1 per day, taken in the early morning. As previously indicated, this is best accomplished when the diet prescribed is relatively low in carbohydrate. Protamine insulin is slow in action because of the slow rate of absorption, and is relatively ill-suited for controlling postprandial hyperglycemia of high degree. Difficulty with postprandial hyperglycemia, however, is most frequently encountered after breakfast, and may be overcome by various means, examples of which may be seen in the preceding brief case reports:

1. By increasing the size of the dose. This is occasionally satisfactory, but tends to produce a low blood sugar during the night. Possibly an insulin with a 30-hour action might improve this situation. In protamine insulin, as at present produced, less than 4% of the insulin is free. A somewhat higher proportion of free insulin might also be valuable for this purpose.

2. By moving back the injection time 1, 2 or 3 hours before breakfast, thus allowing time for a larger amount of protamine insulin to be absorbed.

3. By reconstituting the diet so that little of the carbohydrate appears in the breakfast, and most in the evening meal.

4. By the use of a dose of regular insulin, combined with protamine insulin. Contrary to the experience of some, we have been successful by using a long, narrow-bore syringe, and some care in avoiding mixing of the fluids, in giving the two insulins in a single injection.

5. By the use of a second overlapping dose of protamine insulin, given some hours after the morning dose, so that a portion of it is being absorbed during the postprandial period, that is, at the same time as the free insulin of the following morning dose.

6. By the use of regular insulin in the morning to control the postprandial hyperglycemia, and protamine insulin in the afternoon or evening to control the hyperglycemia of endogenous origin.

Protamine insulin in diminished dosage will sometimes control the blood sugar of the patient quite as effectively as a larger dose of regular insulin. While the effect is not constant, we would estimate the economy of insulin over the series of approximate 30%, a quite substantial saving for some of the poorer patients.

Protamine insulin, however, has an important theoretical advantage, the practical value of which it is still too early to judge. Rest for the injured organ has long been emphasized as an important principle of treatment but, in insulin treatment as commonly employed, one must acknowledge that the main effect obtained has been the suppression of postprandial hyperglycemia. To a large extent it is true that for three-fifths of the day the patient has carried on with the aid of his own insulin production and only when this was

grossly insufficient to control the hyperglycemia of endogenous origin has it received outside support. Too little attention, in our opinion, has been given to the desirability of providing the utmost possibilities for repair and to this factor might be ascribed the so-called inherent progressiveness of the condition. With its prolonged action protamine insulin is much more suitable than regular insulin for substituting in place of insulin used for endogenous metabolism, and accomplishing more complete rest of the pancreas. There is some hope that, particularly in children and those adults recently acquiring an acute form of diabetes, this may be of value in protecting and improving the carbohydrate tolerance of the patient.

Summary and Conclusions. Our experience with protamine insulin confirms the view that it is a distinct contribution to the effectiveness of antidiabetic therapy. When possible, we prefer to administer it in a single morning dose. Various methods of using it alone and in combination with regular insulin are illustrated and discussed.

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INCIDENCE AND DIFFERENTIAL DIAGNOSIS OF HYPOGLYCEMIC CONVULSIONS.

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THE discovery of every new etiologic agent for convulsions demands a search among epileptics to determine the frequency of this agent. In recent years much attention has been given to hypoglycemia as a convulsive factor, particularly in association with

instances of hyperinsulinism. The present study aims to determine the frequency of this factor in a series of 200 consecutive patients with recurrent seizures. Differential diagnostic features between hypoglycemic epilepsy and other epilepsies are also submitted.

Material and Method. The subjects of this study attended the Out-patient clinics for epilepsy at the Los Angeles County General Hospital and the Cedars of Lebanon Hospital. They all received the following routine investigation: complete history, general physical examination, neurologic examination, urinalysis, blood count, blood Wassermann test, Roentgen ray of the skull and spinal fluid examination. Special tests, such as electrocardiography and encephalography, were performed when indicated. On the basis of these examinations there were shown to be 113 cases of epilepsy of unknown etiology and 87 cases of known etiology; the most common causes among the latter being: trauma, lues, encephalitis, birth injury, and alcoholism. None of the patients were on phenobarbital therapy or treatment of any other type previous to the period of testing.

The patients were requested to refrain from eating during the 36 hours preceding examination: from supper of one day to after breakfast of the third day. A fast of this duration was deemed advisable, since one of our patients¹ with hyperinsulinism failed to develop symptoms of hypoglycemia until 20 hours after her last meal. The usual overnight fast would have been ineffective in disclosing her abnormality. The patients were allowed water as desired throughout the fast. Smoking was interdicted, since nicotine is said to elevate the blood sugar. Relatives or friends were instructed to keep the patients under observation and to report any untoward developments. The time of occurrence of convulsions and of petit mal was noted. The patients were examined at the end of the fast for hypoglycemic manifestations and a specimen of venous blood was obtained for a quantitative glucose determination. The Benedict method² was used for all sugar analysis, the Folin filtrate being prepared within 20 minutes after the blood was drawn. Observations on 2 cases of pancreatic islet cell adenomas were the basis of comparison between the convulsive phenomena of known hypoglycemic origin and those of other epilepsies.

Results. Only 31 patients (15.5%) of the 200 tested, presented blood sugar readings below 70 mg. and only 4 (2%) below 60 mg. (Chart I). In none of these were there objective symptoms suggesting hypoglycemia. Five patients had either tachycardia or perspiration or both but the lowest blood sugars were 67 and 68 mg., the others being well over 70 mg. Although a few blood sugars were lower than the average normal and although a few other cases showed mild hypoglycemic (?) symptoms without reduced blood sugars, no diagnostic weight can be attached to these instances as evidence for the hypoglycemic origin of the convulsions. Therefore, although a few blood sugars were lower than the average normal there were no definite hypoglycemic manifestations.

Following a convulsion the blood sugar may be elevated to normal or higher levels. Hence the absence of hypoglycemic symptoms or of a low blood sugar after a convulsive attack does not exclude the hypoglycemic origin of the latter. Convulsions occurred during the fast in 18 instances. That these were spontaneous rather than the result of hypoglycemia is shown by:

1, the absence of low blood sugar determinations. (Most attacks occurred sufficiently early in the fast to exclude the transient postconvulsive rise in blood sugar), or

2, the frequency of attacks (daily in $\frac{1}{3}$ of these patients), or

3, the absence of convulsion on repetition of the fast (Table 1). Likewise the petit mal attacks which were recorded during the fast in 15 cases were of every-day occurrence in these patients (Table 2), and the blood sugar in every instance was within normal limits.

It may be concluded, therefore, that fasting for 36 hours failed to reveal a single instance of clinical symptoms resulting from hypoglycemia in 200 consecutive epileptics.

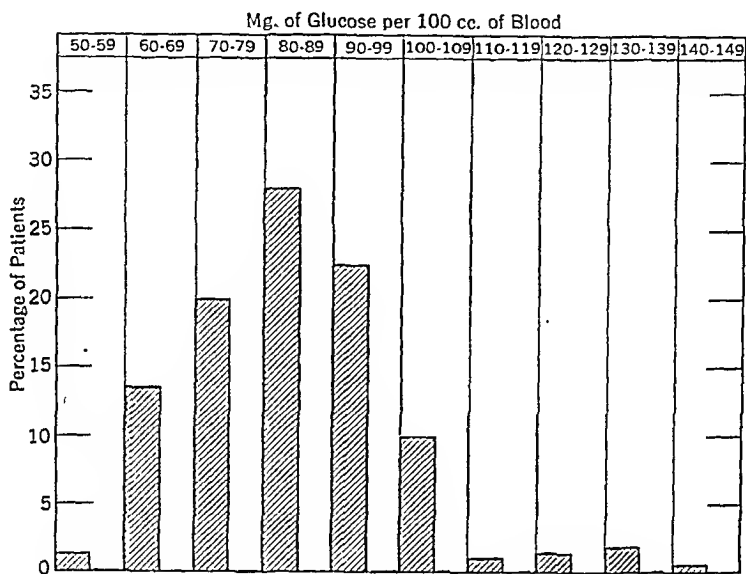


CHART I.—Distribution of 36-hour fasting blood sugars for epileptics.

The Validity of Fasting as a Test for Hypoglycemia. Blood sugar is maintained at a fairly constant level by a homeostatic mechanism including a number of different physiologic factors.³ In certain pathologic states, the normal mechanism may be altered so that the blood sugar in the postabsorptive state is constantly below normal. Here the carbohydrate level is persistently depressed at all times except subsequent to the ingestion of food when it may become temporarily elevated to normal or higher.* This is the usual condition in the clinical instances of hypoglycemia with which we are conversant, such as pancreatic adenomas, pituitary cachexia and hepatic disease. Hence, in these cases, it suffices for diagnosis

* Other physiologic factors may intermittently overcome the hypoglycemia, but of these we have relatively little information.

merely to withhold food and permit the blood sugar to drop to a subnormal level.

TABLE 1.—RECORD OF GRAND MAL APPEARING DURING THE FAST.

Case No.	Subject.	Diagnosis.*	Hours of fast when attacks occurred.	36-hour fast—blood sugar, mg. %.	Hypoglycemic symptoms.	Spontaneous incidence of grand mal.	Repetition of test.	
							36-hour fast—blood sugar, mg. %.	Symptoms.
2	H. A.	I	{12 24}	78	0	2-4 per day		
9	T. B.	O	30	89	0	"Frequent"		
26	J. C.	I	20	88	0	1 in 4 months	65	0
34	R. C.	I	36	93	0	4-5 per day		
65	E. F.	E	{36 24}	93	0	2-3 per week	79	0 (24 hours)
69	W. G.	I	25	69	0	1-3 per month		
76	J. G.	I	23	83	0	7 in 5 years	105	0
83	A. G.	I	7	82	0	1-2 per week	67	2 convulsions
							95	0
							71	0
							105	0
86	J. H.	Ec	34	89	0	5 per day to 2 per month	78	0
95	N. H.	I	32	73	0	1 per month	87	0
99	H. H.	I	30	104	0	5 per month	84	0
113	A. K.	I	36	108	0	Daily		
132	M. M.	I	{24 1}	91	0	Daily	73	0
152	C. P.	I	26	69	0	1 per year	83	Convulsion
153	J. P.	T	23	77	0	2 per month		
155	A. P.	I	{18 36}	94	0	1 per week	75	0
158	F. P.	E	{25 24}	91	0	1-2 per month	{59 78}	0 0
177	J. S.	I	31	67	0	Daily	75	0

Theoretically, at least, it is conceivable that there are transient states of hypoglycemia in which the homeostatic mechanism is only temporarily overcome. In such transient states, fasting may fail to bring the pathologic condition to light. The etiologic factor may not be operative during the test period or, being active, may have dissipated itself so that the blood sugar has returned to normal by the end of the fast. To establish pathologic states of this type, our 36-hour fast has obvious deficiencies. However it is unlikely that such temporary hypoglycemic phases are actual factors in epilepsy.

First, we were unable to find a report of any such paroxysmal states which had produced major hypoglycemic symptoms. We did find two instances^{4,5} in both of which the fasting blood sugars were normal but hypoglycemia with symptoms occurred several hours after eating. The symptoms were however mild and the hypoglycemia of relatively slight degree. On the other hand, a moder-

ately severe degree of hypoglycemia is necessary for the production of convulsions. Therefore it would appear improbable that a disturbance of the carbohydrate regulating mechanism of this degree would occur spontaneously or repeatedly without some indication in the fasting blood sugar. Such would seem to be the case, since no instances of the more severe symptoms such as coma, convulsions, or confusion on a hypoglycemic basis without a low fasting blood sugar were found in the literature.

TABLE 2.—RECORD OF PETIT MAL APPEARING DURING THE FAST.

Case No.	Subject.	Diagnosis.*	Hours of fast when attacks occurred.	36-hour fast—blood sugar, mg. %.	Hypoglycemic symptoms.	Spontaneous incidence of petit mal.	Repetition of test.	
							36-hour fast—blood sugar, mg. %.	Symptoms.
10 . . .	E. B.	I	..	91	0	Daily		
46 . . .	H. C.	L	32	75	0	Daily		
58 . . .	L. E.	I	36	85	0	2-3 per day		
59 . . .	J. E.	A	29	92	0	10 per day		
77 . . .	G. G.	T	33	98	0	6-7 per day		
84 . . .	J. H.	L	..*	86	0	1 per day		
90 . . .	J. H.	I	32	63	0	3-4 per day	77 59	0
96 . . .	J. H.	O	24	141	0	1 per day		
100 . . .	R. H.	I	24	82	0	0-4 per day		
102 . . .	A. I.	I	24	125	0	10-20 per day		
104 . . .	A. I.	I	24	66	0	Several daily		
117 . . .	E. L.	I	20	66	0	1-2 per day	51 83	0
125 . . .	P. L.	E	24	106	Pulse 108	Several per day to few per month		
181 . . .	M. S.	I	32	69	Pulse 120	"Numerous"	98	
185 . . .	D. S.	I	..	83	Head-ache	Few per month		

* 7 attacks.

Code for diagnosis: A = alcoholism; Ec = eclampsia; E = encephalitis; I = idiopathic epilepsy; L = lues; O = organic, but not otherwise diagnosed; T = trauma.

Second, in the best known example of this type of transient hypoglycemia, namely, that following a meal rich in carbohydrate, such as the glucose tolerance test, hypoglycemic symptoms are conspicuous by their absence or at best are very mild. We know of no clinical case of hypoglycemia in which pathologic manifestations, particularly of the moderate or severe type, were present during this phase of the glucose tolerance test and not during fasting. It is of interest to note that the distribution of blood sugar in 92 epileptics 4 hours after eating, reported by Tyson, Otis, and Joyce,⁶ was very similar to that obtained in our 36-hour fast (Chart I). One may conclude

then that transient clinical symptoms of hypoglycemia of the type postulated above is very uncommon. One must take into account those physiologic forces tending toward the maintenance of a normal blood sugar which might readily counteract the effects of an intermittent hypoglycemia-producing lesion. It may be that only when this pathologic tendency is persistent and continuous that the neutralizing effects of the homeostatic mechanism are overcome and hypoglycemia becomes apparent. Although the demonstration is lacking for transient hypoglycemic states productive of major symptoms, their existence as an etiologic factor in epilepsy is not thereby excluded. There is, however, a bit of further evidence which makes this possibility, at least as a frequent occurrence, quite unlikely. The injection of insulin in 40 of our epileptics,⁷ in dosage sufficient in most instances to depress the blood sugar to very low levels, failed to result in the reproduction of the seizures. It is this experimental induction of the paroxysmal hypoglycemic state with its negative results in epileptics which makes it appear improbable that transient hypoglycemia is a frequent etiologic factor in convulsions. On the basis of these considerations, fasting appears to be a valid method for the detection of hypoglycemic epilepsy.*

Differential Diagnosis of Hypoglycemic from Other Types of Convulsions. Fasting is not the only means of differentiating hypoglycemic from other types of convulsions. The history of the attacks may be very important. We have observed numerous hypoglycemic attacks in 2 cases of hyperinsulinism with convulsions due to proven adenomas of the pancreatic islets. The following diagnostic suggestions are based on observations in these 2 patients.^{1, 8, 9}

Hypoglycemic symptoms in the period preceding the convulsions are of great diagnostic significance when they occur. The different prodromal symptoms are numerous and may vary from one attack to another. The symptoms are those which have been described by many observers as occurring with insulin overdosage and the more common symptoms are: hunger, sense of ill being, weakness, palpitation, tremor, perspiration, confusion, restlessness and various focal neurologic symptoms. Occasionally both of our patients had convulsions without any apparent prodromal symptoms. Sometimes the interval between the first symptoms and the convulsion was several hours. In our patient (S. A.), one or

* One might wish that a greater degree of correlation had been demonstrated between the symptoms and the low blood sugar in these cases. In all minor degrees of hypoglycemia, one should be particularly careful in arriving at conclusions. Many instances of low blood sugar without symptoms occur as an isolated finding in normal persons. Again, fasting blood sugar values in the same individual vary on different days. This may be due to diet and possibly many other factors. We believe that in all borderline cases of hypoglycemia there should be demonstrated: 1, a low blood sugar during two or more consecutive attacks of symptoms; 2, relief of the symptoms by the administration of carbohydrates during the attack, and 3, higher or normal blood sugar values between symptoms. In the absence of any of these postulates, proof is lacking that hypoglycemia is the etiologic factor.

several of the following symptoms might precede a convulsion: a sense of impending danger, palpitation, tremor, profuse perspiration, headache, vomiting, confusion, restlessness, involuntary singing, anomial asphasia, numbness of the right hand, and twitching of the right face. Our other patient (I. M.), also had prodromal periods which varied as to duration and content. Several times she was facetious and coquettish, at other times restless and even maniacal; once she beat her son unreasonably and again she was hallucinatory for the greater part of the day. Therefore, prodromal hypoglycemic symptoms, though not constant, are an important diagnostic aid.

One hypoglycemic symptom we believe calls for special comment. *The occurrence of profuse perspiration before an epileptic seizure should strongly arouse suspicion of an underlying hypoglycemia.* The physician who sees the prominent beads of sweat as they stand out on the body in a spontaneous hypoglycemic attack or following the injection of insulin cannot help but be impressed with the diagnostic significance of this finding. A fair number of epileptics, and possibly all, perspire during major seizures; but this is certainly not due to hypoglycemia because the blood sugar is increased during a convulsion. The feature of particular significance for the hypoglycemic convulsions is profuse perspiration during the prodromal period or its occurrence in hypoglycemic attacks unassociated with seizures.

Mental confusion for a variable period preceding the convulsion is another symptom which should suggest hypoglycemia. This occurred often in both of our patients and has been frequently reported in the literature. This is uncommon in other types of epilepsy. In the prodromal periods of longer duration, it is possible to verify the diagnosis by a blood sugar determination before the convulsion occurs. Not all premonitory symptoms in epileptics are due to depressed blood sugars; however their presence, particularly if of the hypoglycemic variety, warrants an investigation of the blood sugar concentration.

Variability in the attacks is also an aid to diagnosis, since the character of the hypoglycemic attacks varies from time to time, whereas in other epilepsies the attacks tend to be of the same types. S. A. had various attacks, consisting at different times of convulsions, coma, somnambulism, twitching about the right eye, numbness of the right hand, hemiparesis, anomial aphasia and states of confusion, extreme restlessness, involuntary crying, laughing, and singing, or delusions and hallucinations; alone or in combination. A similar, though less varied group of paroxysmal hypoglycemic episodes appeared in the case of I. M. Besides these different types of attacks, the convulsions varied much in severity and in the totality of their manifestations. There might be only the aura, or twitching of only one or more members on one side of the body, or a generalized seizure, with or without stupor or mania. When the

hypoglycemic patient is seen soon after the first or the first few attacks this variability will not be apparent. Even in cases of longer duration, it will probably be necessary to receive a report from some relative or friend who has observed a number of the attacks. Furthermore the latter *are often* atypical, particularly since unconsciousness may accompany only minor motor manifestations. In epileptics, as a rule, minor degrees of motor disturbance, *e. g.*, myoclonic twitches, are not accompanied by any impairment of consciousness. In the patients with hypoglycemia, minor phenomena, *e. g.*, rolling of the head, twitches about the face, and isolated loss of bladder control are often accompanied by loss of consciousness. The attacks may be atypical in other respects also. This does not mean, of course, that classical grand mal seizures do not occur with hypoglycemia. More observation is needed on this point. In the general group of epileptics the individual patients average one, two or at best three different types of attacks, grand mal, petit mal, automatisms; the numerous variable attacks seen in hypoglycemia are not encountered. Although it is conceivable that in some instances of hypoglycemia the paroxysmal episodes will all happen to be the same, such will probably be the exception. Conceivably some other etiologic agents for convulsions may also produce a great variety of different paroxysmal phenomena, but in regard to these we have very limited data and at least they are not common. Variability, both qualitatively and quantitatively, in the nature of the attacks of epileptics should suggest a hypoglycemic origin.

Finally, the relation of attacks to feeding is very important. The longer the interval since the preceding meal, the greater the likelihood of hypoglycemic symptoms. Convulsions occurring only during the early morning or before breakfast should particularly arouse one's suspicion, especially if the patient has profuse night sweats or is frequently confused on arising in the morning. Hypoglycemic symptoms have been recorded also as occurring late in the afternoon or late in the morning, at times when nocturnal or early morning symptoms are not stated to be present. This again brings out the remoteness of the symptoms to the previous feedings. It may also indicate that the postprandial hypoglycemia is more marked than on fasting. However, the same symptoms during the night may pass unnoticed, though there may be additional factors during the waking state which tend to make for a greater degree of hypoglycemia, *e. g.*, muscular activity. In both of our patients with hyperinsulinism attacks were most numerous during the early morning hours and there were frequent periods of confusion when the patient was awakened for breakfast. In the case of A. S., night after night, the nurse's chart read "profuse diaphoresis, change of linen necessary" at 2 A.M., and 5 A.M., at which times he was aroused for feedings. Obviously not all nocturnal or early morning attacks are to be ascribed to hypoglycemia. Still all patients with

this history, especially if there are no attacks at other times, should be investigated for depression of the blood sugar level.

The following points in the anamnesis may therefore be regarded as suggestive of a hypoglycemic origin for convulsions: 1, a premonitory period with hypoglycemic manifestations; 2, variability in the character of the attacks, and 3, remoteness of attacks from the preceding meal.

Although suggestive, there is nothing specific in these factors for diagnosis. Suspicions aroused on the basis of history in regard to the above points should be verified by an attempt to reproduce the attack through fasting for 36 hours. If symptoms arise during the fast, the blood sugar should be determined at that time. In the absence of suggestive symptoms, hypoglycemia may be excluded. In clinical practice where the complete investigation of the average epileptic involves the expenditure of much money on tests which are of positive value in only a few instances, the routine additional expense of a blood sugar determination may not be warranted. The procedure described will enable the physician to exclude the negative cases and select suggestive ones in which further chemical tests are indicated.

The glucose tolerance test is often referred to as an aid in the diagnosis of hypoglycemic states. In this connection two features in these tests have been taken into consideration. The first treats with the height and character of the curve in the average 3-hour test. In this test a high or diabetic curve is accepted as indicative of decreased tolerance, and a low curve of increased tolerance, the so-called flattened curve of hypoglycemia. Yet in proven cases of hyperinsulinism the glucose tolerance test is often normal or at times, even elevated. On the other hand, tests performed on many patients not suffering with hypoglycemia reveal depressed or flattened curves. The second feature of the glucose tolerance test refers to the low blood sugar readings obtained on the 4th, 5th and 6th hour specimens. The actual limits of the normal depression in the blood sugar at these intervals has not been definitely established. Furthermore, isolated low blood sugar readings in these specimens, if unassociated with other confirmatory findings, are questionable evidence that symptoms are due to hypoglycemia. It appears logical to us to insist that, if the depressed sugar reading is to be the basis for attributing the clinical picture to hypoglycemia, the patient's complaint or other unmistakable hypoglycemic symptoms should be present when the low blood sugar is obtained. We have already referred to our inability to find a single clinical instance of moderately severe hypoglycemia in which the diagnosis was established in this manner. Suffice it also to say that in a series of epileptics, on whom 4-hour glucose tolerance tests were performed, hypoglycemic symptoms were unusual and convulsions were not reproduced in a

single instance.¹⁰ Therefore glucose tolerance tests showing either a low, "flat," curve or a low blood sugar in the 4th, 5th or 6th hour specimens without the reproduction of symptoms cannot be accepted as diagnostic of clinical hypoglycemia. Nevertheless the fall in blood sugar subsequent to the ingestion of carbohydrate is usually greater than that observed on the overnight fast. In the future a valuable test may be worked out on this basis. At present no test of this character is available.

The response to the injection of insulin has been suggested as a diagnostic measure in suspected instances of hypoglycemia. For the present, one must admit that the test has not been standardized nor the validity of the method demonstrated in known cases of hypoglycemia.

A careful history directed toward suggestive features, *e. g.*, variability of the attacks, prodromal symptoms of hypoglycemia, and the remoteness of attacks from the preceding feeding, plus the attempt to reproduce the attack by fasting, represent important procedures for the diagnosis of hypoglycemic epilepsy. Obviously the chemical demonstration of a low blood sugar is an additional and most valuable corroboration. Still one must recall that unless searched for some time after a feeding diminution of the blood sugar may be absent. Immediately after a convulsion it may be absent also.

Summary and Conclusions. 1. Two hundred consecutive epileptic patients subjected to a 36-hour fast failed to develop clinical symptoms of hypoglycemia in a single instance.

2. In 2 patients with hyperinsulinism the attacks were variable in nature, often preceded by obvious signs of hypoglycemia and most frequent after the longest interval without food, *i. e.*, during the night or early morning. The most constant method for revealing the attacks was the with-holding of food.

3. On the basis of the foregoing, the following diagnostic criteria for hypoglycemic convulsions or epilepsy are suggested:

a, Variability in the nature of the attacks, prodromal symptoms of the milder hypoglycemic type, and the occurrence of attacks at times remote from the last feeding should suggest a hypoglycemic origin.

b, A 36-hour fast should then be prescribed, for the purpose of reproducing the attacks, or at least, of revealing obvious signs of hypoglycemia, and

c, A fasting blood sugar determination preferably at the time of earliest symptoms should be obtained. The latter is unnecessary in the absence of symptoms on fasting.

We are much indebted to Dr. Newton Evans and Dr. A. H. Zeiler for the coöperation of their laboratories. To Dr. Samuel Ingham, Chief of the Neurologic Service, we wish to express thanks for helpful criticism and stimulation in this study.

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SUPPLEMENTAL REPORT OF A CASE OF ESSENTIAL PENTOSURIA OF TWENTY-EIGHT YEARS' STANDING.

(WITH A STUDY OF THE SPECIFIC PENTOSE PRESENT.)

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ESSENTIAL pentosuria is not as uncommon as was once supposed, but is still sufficiently obscure to warrant reports of individual instances. The present paper continues in brief the history of a case (the 22d on record) reported in 1909,¹ and adds *inter alia* a recent chemical demonstration of the specific pentose present. Clinical details need not be repeated.

Case Report. In March, 1908, the patient, an active lawyer, then aged 50, was denied life insurance on the finding of sugar in the urine. A study by the reporter indicated that the reducing substance in the urine was pentose, and this finding was confirmed by Prof. Charles H. LaWall,² who obtained positive responses to the phloroglucin- and orcin-hydrochloric acid tests, and precipitated by the phenylhydrazin method characteristic pentosazone crystals, which, when purified, had a melting point of 157° C. Dextrose was negatived by the indigo carmin test; the fermentation tube showed no evolution of CO₂ during 24 hours. The sample was optically inactive on nearly every occasion, but once or twice there was a slight

dextrorotation, attributed—perhaps erroneously—to transient alimentary glycosuria not otherwise shown.*

Twenty-eight years have passed; the patient has been (and is) extraordinarily energetic and active, physically and mentally. Although he refuses to undergo any prolonged dietetic studies or controlled blood sugar observations, he is not entirely inoperative, and we have been able to make a number of isolated blood sugar estimations, of which the following are instances: Blood counts were, and are, within normal limits of variation. All tests for lues have been negative, and there is no luetic history. The attempt to detect pentose in the blood was made twice and recently was positive. The patient has had, from time to time, minor ailments of no special significance, unless importance be attached to recurrent attacks of colitis and outbreaks of podagra. In connection with the latter, it may be noted that the uric acid content of the blood shows a constant tendency to exceed 4 mg. per 100 cc.

	Sugar.	Urea N.	N.P.N.	Uric acid.		Urine	Pentose
		Mg. per 100 cc. blood.			B.M.R.	%.	24 hr. output.
January, 1918	110						
March, 1925	140						
September, 1928	84	14	26	4.1			
January, 1931	104	-8	0.71	10.5 gm.

Chemical Observations. In 1900, Neuberg,³ who isolated racemic arabinose from the urine of a pentosuric, reported that this sugar was optically inactive, and that an osazone was produced with diphenylhydrazin. Elliott and Roper⁴ (1912) reported a case in which the specific sugar in the urine yielded with phenylhydrazin, a crystalline osazone, the latter, in a pure condition, melting constantly at 163° to 164° C. They were unsuccessful in their attempts to prepare other derivatives of the sugar with diphenylhydrazin or with *p*-brom and *p*-nitrophenylhydrazin. A case similar to Neuberg's was described by Aron,⁵ in 1913; and Cammidge and Howard⁶ reported the pentose in their cases as racemic arabinose.

In 1914, however, Levene and LaForge,⁷ found a dextrorotatory pentose which did not form a di-phenyl osazone, and which they regarded as xyloketose on the basis of the following observations:

1, When the dextrorotatory pentosazone was mixed with levorotatory xylosazone its melting point increased by 42° C.;

2, The character of the mutarotation of the osazone was peculiar in that the initial rotation was lower than the equilibrium rotation;

3, On standing, the optical rotation of the urinary osazone increased in magnitude;

4, A dextrorotatory xylosazone may be derived from (a) *d*-xylose, (b) *l*-lyxose or (c) from the ketopentose corresponding to these two aldoses. The pentose in the urine was dextrorotatory so that it could not have been *d*-xylose, which is levorotatory; and it differed from the latter in the properties of its *p*-bromphenylhydrazone;

* In several cases of pentosuria, it has been established on what appears to be conclusive evidence that while the urinary pentose was optically inactive the apparently neutral urine yielded a dextrorotatory osazone; and in certain instances a dextrorotatory urinary pentose has been reported.

5, The melting points of both the urinary pentose and *d*-xylose were almost identical, but when the two substances were mixed, the melting point of the mixture was depressed below that of either substance alone.

From all this, Levene and LaForge⁷ concluded that the urine pentose was not xylose. Only two other explanations of the structure of the urine pentose were possible: (a) *l*-lyxose and (b) *l*-ketolyxose (*d*-ketoxylose). The former was ruled out on the basis of the differences in the properties of the *p*-bromophenylhydrazone. The structure of the urinary sugar as that of a ketopentose corresponding to *l*-lyxose or *d*-xylose (Fischer's nomenclature) was confirmed also, by oxidation experiments, and specifically by the action of nitric acid and bromine respectively, on the urine pentose.

Zerner and Waltuch⁸ recovered a similar substance from the urine of their 2 cases. The melting point of the pentosazone which they obtained was 162° C. and when mixed with *l*-xylosazone, a new compound (*dl*-xylosazone) was formed, which melted at 210° C. They concluded that the urinary sugar was probably a member of the xylose group. In 1930, in his description of 4 cases of pentosuria, Greenwald⁹ furnished further proof of the existence of xyloketose in urine, as did Hari¹⁰ in his 5 cases. Three years later Enklewitz and Lasker¹¹ reported 12 cases of pentosuria in which the sugar present was established as *l*-xyloketose. In fact these authors assert that this pentose "is by far the more common sugar, if indeed not the only one" in cases of pentosuria.

It appears, therefore, that Neuberg,³ Aron⁵ and Cammidge and Howard,⁶ believed that the pentose in their cases was racemic (inactive *dl*-) arabinose, while Levene and LaForge,⁷ Zerner and Waltuch,⁸ Hiller,¹² Greenwald,⁹ and Enklewitz and Lasker,¹¹ describe the urinary sugar in their cases as *l*-lyxose or the corresponding xyloketose. In 1909,¹ when our case was reported, the specific pentose in instances of essential pentosuria was not often determined; but it was assumed from the reports in the few cases in which the specific observation had been made, that invert arabinose was the only urinary pentose in essential cases. The apparent exception reported by Luzzatto¹³ was attributed by some to a transient alimentary pentosuria accompanying the essential form.

Specific Pentose Present in Case Here Reported. On 3 different occasions during the past year, large volumes of our patient's urine were collected. These samples reacted as nearly as could be determined, in a manner similar to that reported in the recent literature of pentosuria. Benedict's¹⁴ quantitative and qualitative solutions were reduced by the urine at room temperature (urine added to 5 cc. Benedict's qualitative solution and allowed to stand for several hours without heating—reduction was apparent). Fermentation did not occur with pure cultures of yeast (*Saccharomyces cerevisiae*) nor when the yeast cake on the market was employed. When 2 to 3 cc. of urine were heated with 4 to 5 cc. of Bial's reagent, a green color was produced. Tollen's phenylglucitol-hydrochloric acid reaction was positive.

Quantitative sugar determinations were made on the urine, employing both Benedict's¹⁴ method and that of Lasker and Enklewitz.¹⁵ In the former technique a known amount of Benedict's quantitative solution to which was added some sodium carbonate was titrated at boiling temperature with either undiluted or diluted urine. The sugar content by this method was found to be 0.22 gm. per 100 cc. of urine.

Lasker and Enklewitz¹⁵ believe that their technique may be used to distinguish a xyloketosuria from a possible arabinosuria. They state that *dl*-arabinose added to normal urine does not react, whereas it is possible to detect 0.05% of added xyloketose, negative results being obtained also with urine containing 4% glucose. In the method of Lasker and Enklewitz¹⁵ the volume of urine (V_1), required to reduce 2 cc. Benedict's quantitative sugar reagent at boiling temperature was determined. In a series of test tubes (12 mm. diameter), there was placed 2 cc. Benedict's quantitative solution, $\frac{1}{2}$ gm. anhydrous sodium carbonate and various amounts of urine, starting with (V_1), and increasing the amount in each successive tube by 0.1 cc. The tubes were well shaken and placed in a water bath at 55° C. for 10 minutes. The tube containing the least amount of urine sufficient for complete reduction was then taken as the end point. The volume of urine used in this tube was designated as V_2 and was employed in the following calculation—

$$(1) \% \text{ xyloketose} = \frac{0.0033 \times 100}{V_2}$$

where V_1 = cc. urine to reduce 2 cc. Benedict's solution at the boiling point.

V_2 = cc. urine to reduce 2 cc. Benedict's solution at 55° C.

0.0033 gm. xyloketose is required to reduce 2 cc. Benedict's solution.

This is Greenwald's equivalent (*i. e.*, -1.22 mg. glucose equivalent to 1 mg. xyloketose by Benedict's method).

$$(2) \text{ grams xyloketose in 24 hours} = \frac{0.0033 \times V}{V_2}$$

where V = cc. urine voided in 24 hours.

Since ordinarily not more than 1 gm. reducing substance is present in urine, an approximate value for V_2 may be obtained by calculation, according to the following equation:

$$(3) V_2 = \frac{0.0033 V}{(R-1)}$$

where R = grams of total reducing substance per 24 hours. This will yield the range within which to work.

The amount of urinary sugar found by the above technique was .20 gm. *l*-xyloketose per 100 cc. urine.

Preparation of Osazone. A mixture of 4 gm. phenylhydrazin-hydrochlorid and 6 gm. crystallized sodium acetate was dissolved in 500 cc. of urine, and the mixture was heated on a water bath for 1 hour. The solution was then filtered, allowed to cool, and the crystals were recrystallized from 20% ethyl alcohol several times. Upon microscopic examination the osazone crystals were found to consist of long yellow needles in the typical sheaf formation. The melting point was constantly at 157 to 158° (corrected 161.7° C.).

When equal parts of the osazones of *l*-xylose and the urinary pentosazone were mixed, and recrystallized, the racemic xylosazone was formed, as indicated by a rise of the melting point to slightly above 200° C. The racemic variety was formed, however, in but 1 instance and not on 2 other occasions—the samples being from different voidings. The typical-shaped crystals of the racemic type were observed in the positive case when viewed under the microscope. Why the racemic type of crystal was not obtained again is not known.

Optical Activity. 80 cc. of urine were mixed with 20 cc. of ethyl alcohol and several grams of charcoal and filtered. The rotation when read in a 2.5 dm. tube was dextrorotatory.

The osazone of the urinary pentose dissolved in a mixture of 4 cc. of pyridin and 6 cc. of ethyl alcohol yielded a mutarotation, characteristic of xyloketose. The optical rotation increased in magnitude on standing.

Effect of Bromin on the Sugar. The urine and a solution of the partially purified pentose were treated separately with bromin water and liquid bromin for 48 hours. At various intervals the urine, when boiled free of bromin, still reduced Benedict's qualitative solution. This reducing power was lost upon heating with strong acid.

Examination of Blood. On January 13, 1936, a sample of blood was obtained. Bial's Orcinol-HCl and Tollen's Phloroglucinol-HCl tests were found to be positive repeatedly. Spectroscopic examinations revealed the absorption band between D and E; thus narrowing the positive findings down to the pentoses and glycuronic acid. The Naphthoresorcinol-HCl test, as suggested by Tollen,* was negative for glycuronic acid. It is thus possible to conclude that the positive Bial's and Tollen's Phloroglucinol-HCl tests were due to the pentoses. However, sufficient serum was not available to ferment the glucose and then attempt to prepare an osazone. Negative findings were obtained with normal blood specimens used as controls. From these observations we feel that we can present the fact that pentose was found in the blood, though it was not possible, for the reason stated, to determine the specific form.

Conclusion. The urinary pentose reported in the present observations gave an osazone, which, after re-crystallization from 20% ethyl alcohol, melted at 157 to 158° C.† Equal amounts of the urinary pentosazone and the osazone of *l*-xylose were mixed and the mixture on re-crystallization from 20% ethyl alcohol, melted at a temperature slightly over 200° C. The characteristic mutarotation was observed when the urinary osazone was subjected to a polariscopic examination. This reaction excluded the possibility of arabinose or ribose, and limited the choice of pentoses to (1) *d*-xylose; (2) *l*-yxose; or (3) xyloketose.

The rotation of the urine was dextro, thus excluding the possibility of *d*-xylose, which is levorotatory. There was only a slight loss of sugar when the urine was treated with bromin whereas when an aldose is brominated, there is destruction of all of the sugar.

From consideration of the following findings: (1) the melting point; (2) the mutarotation of the pentosazone; (3) the increase of over 40° C. in the melting point of the urinary pentosazone when mixed with xylosazone; and (4) the result of observation with bromin, it is believed that the urinary sugar in this study can be regarded as *d*-xyloketose.

Summary. A man whose urine, when he was 50 years old, had been supposed to indicate glycosuria, was found to have pentosuria.

* Allen's Commercial Organic Analysis, 5th ed., vol. 1, p. 496.

† The observations made by LaWall (op. cit.) in 1908-09 showed typical circular crystals in stellate tufts, having a melting point, when purified, of 157° C. The individual crystals differed from those produced by dextrose or levulose in being "more slender in proportion to their length."

Without dietetic regulation or special treatment, he has retained health, strength and vim for the 28 years following. The urine has been studied with special reference to the specific pentose now present, which is found to be *d*-xyloketose.

A pentose (or a substance behaving chemically as a pentose) was also found in the blood, but owing to the small amount of serum available, its specific form could not be determined.

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PHENOLEMIA AND INDOXYLEMIA.

THEIR ORIGIN, SIGNIFICANCE, AND REGULATION.

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THIS is a discussion of certain of the principles we have ascertained from the work done in our Institute on the origin, regulation and significance of phenolemia and indoxylemia. Marenzi, in his book published in 1933, has fully considered the problem of phenolemia and that of indoxylemia has been dealt with in detail in an article of ours (1935).

Phenolemia. While certain authors (Beeher) only measure the free volatile phenols in the blood, others adopt methods which will

measure the bodies with phenolic groups (phenols, aromatic oxyacids, indoxyl, etc.) and even substances (indol) which give color reactions. Such is the method of Theis and Benedict (1924) modified by Marenzi (1931), using preferably trichloroacetic acid for precipitation of proteins. With the method of Marenzi, the values obtained are the following, measured in mg. per 100 cc. of blood.

TABLE 1.—VALUES FOR PHENOL IN THE BLOOD.

Species.	Author.	Free phenols.	Total phenols.	Combined phenols.
Man	Falsia, 1932	1.59	1.82	0.23
Dog	Marenzi, 1933	1.65	1.84	0.19
Rat	Marenzi, 1933	1.62	1.80	0.18

The phenols in the tissues can also be measured by this technique (Marenzi, 1932) even though no volatile phenols are found (Becher). Marenzi has also studied the amounts in the urine (1931, b)

The blood phenols are products of exogenic origin, absorbed from the intestine, where they are formed by bacterial putrefaction of the aromatic bodies of the proteins. They are found, free and combined, principally in the blood and are eliminated by the kidney.

The amount found in the blood of various parts of the body has been determined by Marenzi (1933, d), who found in 5 chloralosed dogs that the value was slightly higher in the blood of the portal vein than in that of the vena cava or the carotids.

The experiments of Becher (1931) and those of Marenzi and myself (1933, b, d) favor the theory of the intestinal origin of phenolemia. When the kidneys are extirpated there is a rapid and progressive rise in the blood phenols. These come from the intestines, as when the kidneys and intestines are both extirpated (according to Becher), there is no rise in the blood and tissue phenol content; however, Marenzi found a slight rise in both total and free phenol, though much less than when the intestine was intact*). This slight rise in the phenols can be due to reabsorption of phenol produced in the operative stump, which is hardly probable owing to the washing and drainage, or to slight amounts produced in the endogenous metabolism.

Extirpating the intestines, leaving the kidneys *in situ*, Becher found there was diminution and even disappearance of the urinary phenols. Marenzi (1933, b, d) has studied dogs in which I aseptically resected the intestine from the anus (included) to the middle of the stomach which was drained and washed by a continuous drop. These animals received subcutaneous saline injections and so lived 4 or 5 days. The combined phenols (which are formed in the intestine) rapidly disappeared from the blood, while the free and total amounts rose slightly at the beginning, and afterward slowly decreased.

* It must be taken into account that Becher only measures the volatile phenols and that Marenzi measures those which give Moir's reaction, which explains the difference.

In the urine of these animals there was diminution of the free phenol and a still more pronounced decrease of combined phenol (Marenzi, 1933 b, d).

The combination of the phenols occurs in all the organs, but most intensely in the small intestine. In spite of classic opinion, the experiments of Mann and Bollmann (1930) confirmed by Marenzi and myself (Marenzi, 1931, a; Houssay and Marenzi, 1931) show that the liver is not an organ which specially combines the phenols. We injected 1 to 2.5 mg. per kg. of phenol by the jugular vein in dogs with liver and one kidney removed, and observed that the combination occurred normally. When the liver and both kidneys were extirpated the total phenol was not eliminated but the combination occurred without alteration (Fig. 1).

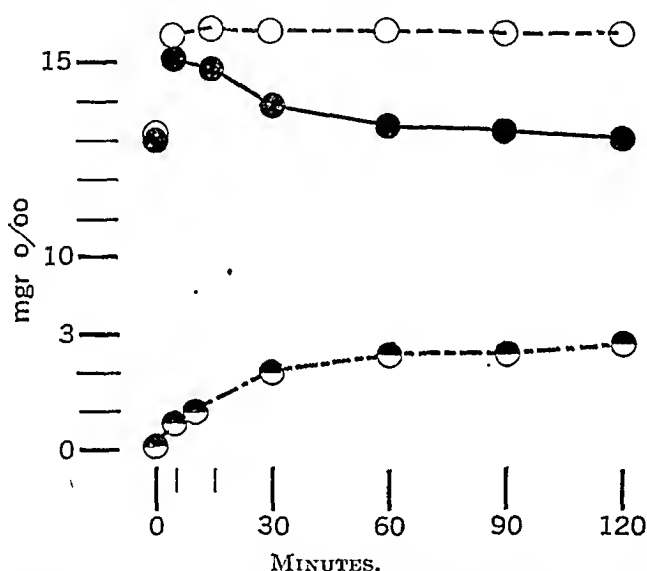


FIG. 1.—Dog, 28 kg., with liver and kidneys removed. At 0 m. 28 mg. phenol is injected in the jugular vein. 0---0, Total phenol in blood; ●—●, free phenol in blood; ●- - -●, combined phenol in blood.

The kidney is the organ which regulates the elimination but not the combination of the phenols. We have said that nephrectomy causes a rapid and progressive accumulation of phenols originated principally, if not totally, in the intestine. If 1 to 2.5 mg. per kg. body weight of phenol is injected into the venous circulation of a recently nephrectomized dog, the phenol accumulates in the blood and does not disappear, but combination occurs well. If the kidney is injured by mercuric bichlorid or uranyl nitrate and there is anuria, or almost anuria, the injected phenol remains in the blood and is not eliminated, or eliminated very slowly (Marenzi, 1931, c). Total extirpation of all the intestine or of the small intestine retards the combination, and the rise in phenol produced by the injection persists longer. On the other hand, extirpation of the large intestine,

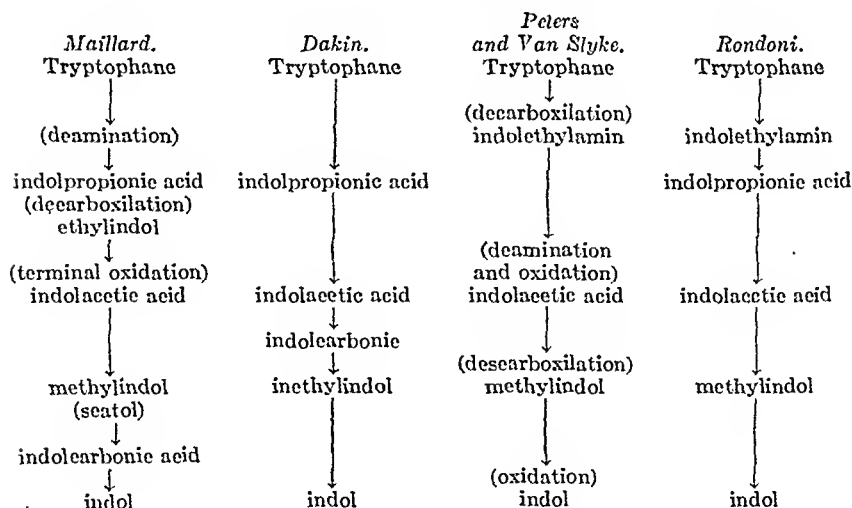
stomach or spleen does not retard the combination (Marenzi, 1931, c, 1933, d).

The amount of phenol increases in the spleen, muscles, kidney, liver, etc., after injection of phenol into the blood stream. The kidney retains the phenols and later eliminates them (Marenzi, 1933, c).

To recapitulate: The phenols of the blood are due to absorption from the intestine of phenols produced by bacterial action, with a probable small quantity produced by endogenous metabolism. The blood is the site for their storage, although they accumulate to a lesser degree in the tissues. The kidney is the essential regulator of the phenolemia, as it eliminates the phenols. The combination of the phenols occurs in many parts of the body but especially in the small intestine, the liver not having any special rôle in this process.

Indoxylemia.* *Indoxyl.* Tryptophane is the precursor of indol (Nencki, 1895; Hopkins and Cole, 1903). The intestinal bacteria transform it into skatol and indol, the presumed steps of this transformation taking place as seen in Table 2. Indol is absorbed and converted by the liver to indoxyl. The indoxyl accumulates almost exclusively in the blood. The kidney is the eliminating organ of the blood indoxyl and therefore the principal regulator of the indoxylemia.

TABLE 2.—PRODUCTION OF INDOL BY BACTERIA OR IN PUTREFACTION.



Indoxyl is isolated from the urine as indican, that is potassium indoxyl sulphate (indolsulphate or potassium, Dakin) and also may occur as indoxylglucuronic acid. Man eliminates per day 0.9 to 36 mg. (Maillard), 10 to 20 mg. (Migliardi), 15 to 25 mg. (Laroche

* We have published a complete study on this subject with bibliographic data, 1935. The classic monograph by Maillard should also be seen.

and Pouneau-Delille) of indoxyl per day. It is diminished in fasting or on a milk diet and increased on a meat diet, also in intestinal putrefactions, of which it is an indicator, but not a quantitative one, and sometimes by constipation, etc. There is no indoxyl in the bile, sweat or cerebrospinal fluid, but it occurs in the blood.

Indoxylogenous Bodies. Apart from indol, ortho-nitro-phenyl propiolic acid (Hoppe Seyler, 1882-1883, etc.) was the only known body capable of being transformed into indoxyl in mammals. Raper has shown that tyrosin can be transformed into indolic bodies in the larvæ of *Tenebrio*. In our experiments with Deulofeu and Mazzocco (1934-1935) we were able to show that other bodies when injected into nephrectomized dogs, gave rise to indoxyl which accumulates in the blood. The average of the experiments with each substance figures in Table 3.

TABLE 3.—INDOXYLEMIA (IN INDICAN, MG. 0/00) OF BLOOD PLASMA OF NEPHRECTOMIZED DOGS RECEIVING 10 MG. PER KG. INTRAVENOUSLY OF VARIOUS SUBSTANCES.

Drug.	Time after injection.						
	0.	15 min.	30 min.	1 hr.	2 hrs.	4 hrs.	8 hrs.
<i>Indol</i>	1.14	10.48	13.72	19.40	28.20	37.00	46.00
o-nitrophenylpropiolic acid	0.99	9.38	13.73	16.36	19.71	27.00	...
β -indolethylamin	1.23	...	8.54	9.94	11.16	12.96	20.29
β -indolaldehyde	1.02	7.28	8.32	9.78	10.00
β -indolpiruvic acid	1.90	...	5.47	6.18	7.03	7.13	16.39
o-nitrophenylacetaldehyde	1.40	...	2.72	2.66	3.76	6.42	9.56
β -methylindol	0.26	1.42	5.27	9.68
α -methylindol	1.00	...	2.46	2.63	3.62	4.60	6.49
<i>Isatin</i>	1.13	...	1.56	1.83	3.17	4.42	8.55
β -indolpropionic acid	0.84	2.06	4.30	5.66
<i>Tryptophane</i>	0.85	...	1.23	1.44	1.15	1.88	2.69
α -indolecarbonic acid	0.46	0.73	0.97	1.20	1.99
β -indolecarbonic acid	0.59	0.92	1.18	1.56
Control (no injection)	0.80	1.18	1.58	1.99	3.05*

* The highest figure was 4.78.

It can be seen, according to the quantity of indol produced, that indol and ortho-nitro-phenyl-propiolic acid come first; 2d, indolethylamin; 3rd, β -indolaldehyde; 4th, β -indolpiruvic acid and ortho-nitrophenyl-acetaldehyde; 5th, β -methyl-indol and β -methyl-indol, isatin; 6th, β -indol-propionic acid (hardly significant results). None of the following substances produce indol: tryptophane α - and β -indocarbonic acids, tyrosin, ortho-nitro-cinnamic acid, ortho-nitro-phenyl piruvic acid, ortho-nitro-phenyl-acetic acid and nitrobenzaldehyde.

We found there were three different physiologic mechanisms for the conversion into indoxyl (Fig. 2) which are:

1. *General, extrahepatic and extraintestinal:* Ortho-nitro-phenyl-propiolic acid causes a large increase in indoxylemia, even in dogs (nephrectomized or not) with extirpation of the liver or digestive tract. In spite of this the liver seems to be an important site for the

elaboration of indoxyl, because the indoxylemic curve rises slower during the elaboration in the hepatectomized dogs (Fig. 2).

2. *Principal and almost exclusive hepatic conversion:* Injection of indol causes an insignificant rise in indoxylemia when the liver is extirpated, but the rise is rapid and large as is usual, when the digestive tract is extirpated (Figs. 2 and 3).

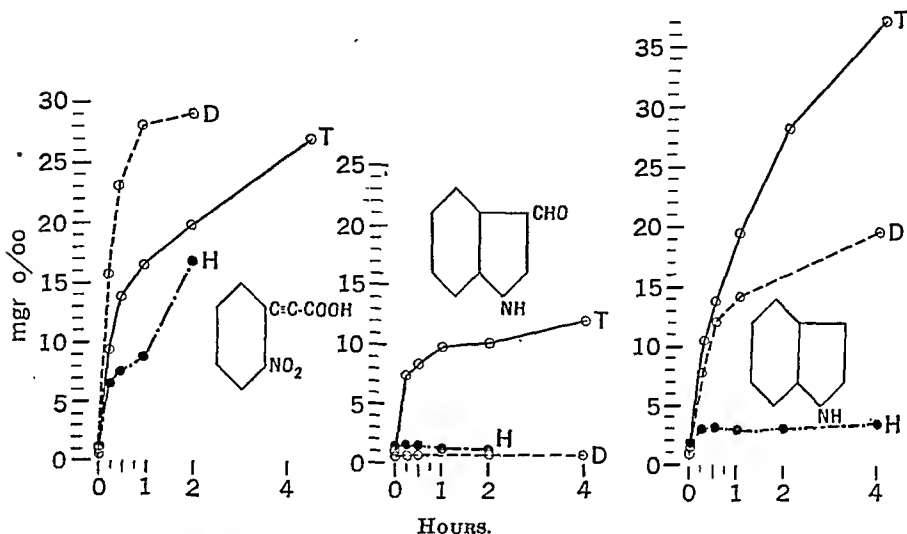


FIG. 2.—Average values of curves of plasma indican (mg. o/oo) in dogs injected in the jugular with 10 mg. per kg. of o-nitrophenylpropionic acid, indolaldehyde, or indol. T, Nephrectomized; D, kidneys and digestive tract removed; H, hepatectomized and nephrectomized. o-nitrophenylpropionic acid is converted into indoxyl even when liver and digestive tract have been removed. Indolaldehyde and many other bodies do not produce indol if the liver or the digestive tract are removed. Indol is converted into indoxyl when the digestive tract is missing, but not in the absence of the liver.

3. *Conversion necessitating both liver and digestive tract:* β -indolaldehyde, o-nitrophenyl acetaldehyde, β -indolpyruvic acid, isatin, β -methylindol do not raise the indoxyl (or the rise is very slight) if the digestive tract or liver are extirpated (Fig. 2). It is probable that the digestive tract forms a precursor, which is probably indol (although with the technique employed we were unable to find this body in the blood after the injection of isatin or nitrophenylacetaldehyde which the liver converts into indoxyl). This mechanism is the most usual, occurring with all the substances except two.

From these experiments it can be deduced, if the intermediate metabolism gives rise to the production of indoxyl (which is not clearly proved), that indolethylamin and indolpropionic, and indolpyruvic acids can be intermediate products, but not the indolcarboxylic acids.

Fate of the Indol. It is possible to measure 1 γ (micro-gram) of indol in the blood (Mazzocco, 1935) extracting it with ether, by the red color which is obtained with para-dimethylamidobenzaldehyde in the presence of hydrochloric acid. We have been unable to

demonstrate indol in the portal or arterial blood of the dog or in the venous human blood whether normal or pathologic, although Becher (1931) found it in the gravest cases of uremia and hepatic insufficiency.

Placed in the small intestine, it is rapidly absorbed and changed to indoxyl in the liver. Up to 5 mg. o/oo of indol can be found in the portal vein during 15 to 45 minutes, which does not pass to the suprahepatic veins unless the absorption is very great and even so the proportion is very much less (Houssay, Deulofeu and Mazzocco, 1935).

The indol injected into the blood disappears rapidly and cannot be traced with ordinary methods after 5 minutes (Olivet, 1929; Gactani, 1933). With more sensitive tests, injecting 10 mg. per kg., it can be measured during 30 to 45 minutes and faint traces found during 2 to 4 hours (Garcia-Blanco and Vidal, 1933; Macchia, 1934; Mazzocco, 1935).

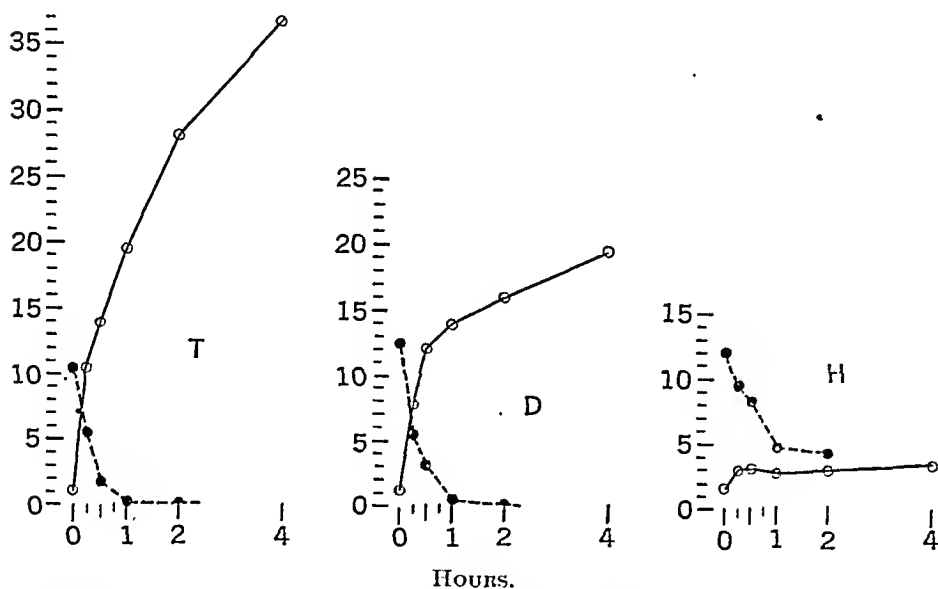


FIG. 3.—Average values of curves of plasma indican (continuous trace) and indol (discontinuous trace) in mg. o/oo, in dogs injected intravenously with 10 mg. per kg. of indol. *T*, Nephrectomized; *D*, nephrectomized and digestive tract removed; *H*, nephrectomized and hepatectomized.

The fixation of indol is accompanied by a rapid conversion into indoxyl, which is almost the same even when the digestive tract is missing, but which ceases if the liver is extirpated. In this case there is a large quantity of indol in the blood after 2 hours (Fig. 3). Contrary to indoxyl, which is accumulated almost exclusively in the blood, indol is retained in the organs where it can be demonstrated (Mazzocco). A large part of the indol is destroyed, as 100 mg. of indol in the blood does not produce more than 30 to 33 mg. of indican in the nephrectomized dog (Houssay, Deulofeu and

Mazzocco, 1935). If 50 mg. of indol is injected, 10 to 20 mg. of indican are eliminated in the urine, *i. e.*, 20 to 40% (Olivet, 1929). A small quantity of indol is eliminated in the urine, bile (Macchia, Garcia-Blanco and Vidal) and saliva (Macchia).

Origin of the Indoxylemia. Indol occurs in the intestine and is absorbed easily, being rapidly converted into indoxyl in the liver, as has been proved in the blood and urine of man and various animals. Unfortunately with the actual methods of estimation, indol cannot be demonstrated in the normal portal blood.

The extirpation of the digestive tract does not modify the conversion of indol into indoxyl in the frog (Gautier and Hervieux, 1907-1919) or in mammals (Houssay, Deulofeu and Mazzocco, 1934-1935) but the extirpation of the liver prevents this conversion (same authors) (Figs. 2 and 3).

The origin of the indoxyl in the blood has been attributed variously as intestinal, septic, metabolic and toxic. The intestinal origin is certain, indoxyluria is an indicator (but not a quantitative one) of intestinal putrefaction; also there is no indicanuria in the recently born or in guinea pigs kept aseptically, and it is less on a milk diet or during fasting but increases on meat diet, etc.

Extirpation of the intestine diminishes and even causes the disappearance of the urinary indican (Becher, 1931; Billi, 1931-1932; Houssay, Mazzocco and Potick, 1934) but later it rises again, which is attributed to bacterial action in the duodenal stump (Billi, Heilmeyer and Pfotenhauser, 1933). Nevertheless we have observed this after extirpating the digestive tract from the cardia to the anus inclusive, draining the cardia and with drop drainage through an esophageal tube (Houssay, Mazzocco and Potick, 1934).

The usual large increase of indicanemia occurring in dogs with extirpation of the kidneys does not take place when the digestive tract is extirpated (Becher, 1931; Billi, 1931-1932). We have observed a slight rise which does not occur when the liver as well is extirpated (Fig. 4). This may be due to a precursor (indol?) stored in the organs or perhaps to the intermediate metabolism. The three groups of investigations agree completely, that the origin of the indol is essentially intestinal. There has been described a rise in the indicanuria in certain septic foci (gangrenes, abscesses, etc.). A septic origin of indoxyl is possible but it has not been proved satisfactorily and much less so the metabolic and toxic origins (Maillard, 1913).

Indoxylemia. Hervieux (1904) was the first to report indoxylemia. Several modern methods, all very similar have been devised for the estimation of indoxyl in the filtrate of serum precipitated by trichloroacetic acid by means of Jolles reaction. We used the method indicated by Mazzocco (1934). Indican is not ultrafiltrable and is not found in the red blood cells, the presence of hemoglobin in serum or plasma makes its estimation impossible.

The following figures have been obtained in normal human blood 0.26 to 0.82 mg. per liter (Haas, 1915-1916-1917); 0.4 to 1.07 (Rosenberg, 1916-1927); 0.16 to 0.64 (Livierato and Simonetto, 1930). The averages found in this Institute are 0.41 (Mazzocco), 0.29 (Biassoti).

It is abundant in the dog and varies considerably, from traces to 2, 4 and 5 mg. o/oo in 181 estimations in this Institute (average 0.68 mg. per liter). We regard as adequate for the experiments the figures obtained between 0.10 and 1.25 mg. per liter.

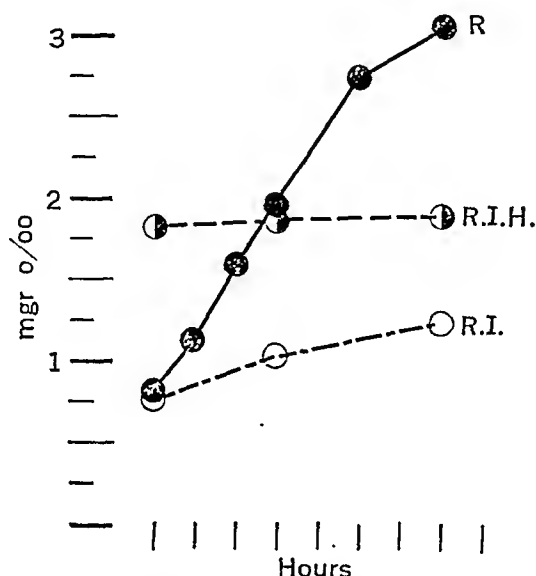


FIG. 4.—Average values of indican (mg. o/oo) in plasma of dogs. *R*, Nephrectomized (10); *R.I.*, nephrectomized, stomach and intestine removed (4); *R.I.H.*, nephrectomized, stomach and intestine removed, hepatectomized (4). Cardia drained and washed by continuous drop in the last two series.

Thyroid or hypophyseal insufficiency does not change the indicanemia. Indoxylemia is above all increased by renal diseases producing uremia. There is no rise in normal pregnancy. In our 1935 paper we summarize the principally known data and the work of Van Slyke and Peters may also be consulted.

From the fact that the indoxyl found in the blood is not an essential product of intermediate metabolism but an exogenous component, the quantity absorbed by the intestine is variable; therefore, the logical thing would be to explore the renal function by means of a new test consisting in the injection of indoxyl into the veins and observing its length of stay in the blood (for example, estimations in series or at a given hour). The dose must of course be innocuous.

Regulation of Indoxylemia. The factors which can regulate the indoxylemia are:

- 1, The quantity of indol produced and absorbed in the intestine.

2, The conversion of the indol in indoxyl in the liver, and its destruction, which is important.

3, Storage in the blood.

4, Elimination by the kidney.

The influence of the condition of the contents and of the mucosa of the intestine on indicanuria has been studied, but little work has been done on the effects of these factors on indicanemia. Laroche, Grigaut and Poumeau-Delille (1929), Laroche and Poumeau-Delille (1932), Laroche and Grigaut (1934) think the intestinal absorption has a large influence on the indicanuria because this rises during peptonic or anaphylactic shock, etc.

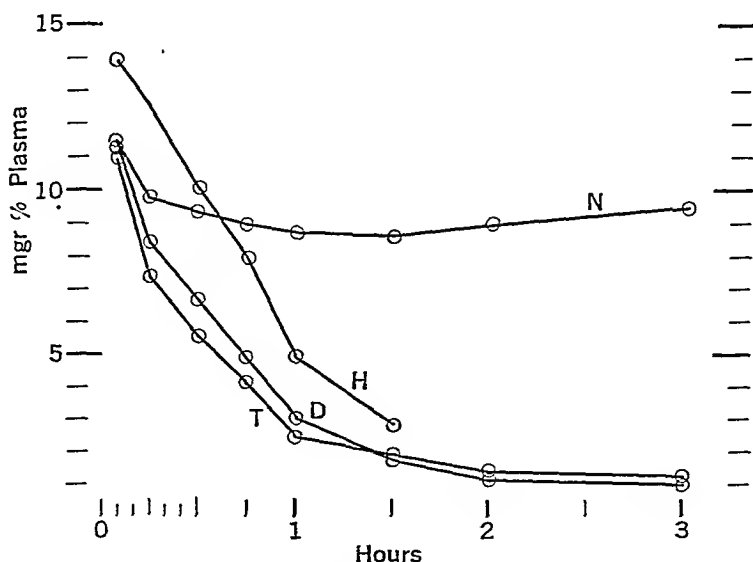


FIG. 5.—Average values of curves of plasma indican in dogs (mg. o/oo) injected intravenously with 2 mg. indican. T, normal controls; D, stomach and intestine removed; H, hepatectomized; N, nephrectomized.

The liver fixes, partially destroys and converts the indol into indoxyl. It is accepted that indicanuria cannot be a test of insufficient hepatic function (Maillard, 1913; Laroche and Poumeau-Delille, 1932). Only in the gravest forms of hepatic insufficiency is indolemia found without hyperindicanemia (Beeher, 1933).

The blood is the principal site for the retention of indican. The organs contain little (Olivet, 1929) or none (Becher, 1920-1921-1931) or small inconstant amounts (Houssay, Mazzocco and Potick, 1934); although if the indicanemia is raised by nephrectomy or injection of indican, estimable amounts may be found (Becher and ourselves). Olivet considers that the liver and skin have a storage capacity, but it must be noted that the amount contained in all the organs is not more than one-tenth to one-seventh of that present in the

blood. Fifteen minutes after injecting indican we found high figures (1.4 to 1.6 mg. per liter) in the kidney, which fixes it for excretion.

The injected indican passes into the urine (Hoppe Seyler, 1883). The elimination begins within a few minutes and is nearly complete in 24 hours, but the total elimination is not obtained until the second day. In dogs, injected with 2 mg. per kg. intravenously, it was sometimes impossible to recover all the dose injected (Houssay, Mazzocco and Potiek, 1934).

The elimination of indican from the blood is performed by the kidney, not by the liver or digestive tract (Houssay, Mazzocco and Potiek, 1934, b.) We injected series of chloralosed dogs with 2 mg. of indican in the jugular vein, which caused a large increase in the indoxylemia. In the controls (Fig. 5, *T*) or those without stomach and intestines (*D*) or without liver (*H*) the indican disappeared from the blood, whereas in the nephrectomized animals (*N*) there was only a slight initial decrease, the indoxylemia then remained high and began to rise slowly after 2 hours, probably due to the endogenous indoxyl. Thus the kidney is responsible for the elimination of indoxyl; it takes it from the blood and rapidly gets rid of it. In the absence of the kidney injected indol remains in the blood.

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CLINICAL OBSERVATIONS AT HIGH ALTITUDE.*

OBSERVATIONS ON SIX HEALTHY PERSONS LIVING AT 17,500 FEET AND A REPORT OF ONE CASE OF CHRONIC MOUNTAIN SICKNESS.

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THE symptoms of acute mountain sickness associated with an ascent of several thousand feet are well known and readily recognized. These symptoms include headache, weakness, nausea,

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vomiting and insomnia. Their usual duration is less than a week and their subsidence is assumed to be related to the phenomenon known as acclimatization. For most persons acclimatization to altitudes as high as 10,000 or 12,000 feet is possible and permanent residence may be accompanied by no other symptom than increased dyspnea on exertion. At these altitudes cities and towns have existed for generations in this country and in others without noticeable impairment of the general health of their inhabitants by the decreased oxygen pressure. Above 12,000 feet the number of permanent settlements decreases rapidly and beyond 14,500 feet there are very few accessible permanent colonies in the world. The maximum altitude at which it is possible for human beings to live for many months in a state of good health varies among individuals, but it is probably under 20,000 feet.¹ Studies on permanent residents living between 14,500 feet and 20,000 feet are few in number and have been confined to the dwellers on the plateaus in central Asia and in the Andes of South America. Notable among these studies are those by Monge² and Hurtado³ concerning the physiologic and pathologic changes observed in men working in mines at altitudes as high as 14,900 feet. The opportunity to extend these observations was afforded this past summer in northern Chile, where studies were conducted in permanent settlements situated as high as 17,500 feet. At this altitude 6 residents, as volunteer subjects, furnished the data which forms a portion of this communication. The remainder of the report is concerned with the discussion of a syndrome which has been designated as chronic mountain sickness. This syndrome was observed in a female patient who had lived for more than 20 years at an altitude of 15,400 feet and at the time of the examination was living at 12,000 feet.

Chronic mountain sickness as a clinical entity was described first by Monge.⁴ Because of this fact the eponymic term Monge's disease has been proposed recently.⁵ This disease is not to be confused with acute mountain sickness, the symptoms of which persist for only a few days, or with "glacier lassitude"⁶ observed in persons residing temporarily at very high altitude. Chronic mountain sickness is observed in persons who are permanent residents at high altitude and by the accepted standards are acclimatized. This acclimatization is relatively permanent and the shortest interval noted by Monge in any of his patients between arrival in the highlands and the onset of symptoms of chronic mountain sickness was 2 years. In other patients the interval was as long as 20 years. The point may be stressed that this is a disease which occurs in healthy persons acclimatized to low oxygen pressures. Among the presenting symptoms are headache, hoarseness, loss of appetite, weakness, paresthesias and transient spells of stupor or coma. On physical examination cyanosis, pigmentation, generalized vasodilatation and hypotension are observed. The syndrome is char-

acterized by remissions following which each relapse is progressively more severe. When the disease develops at a given altitude, ascent to a higher one is associated with an exacerbation of symptoms, while descent to a lower altitude is associated with relative or complete alleviation. If the patient remains in the highlands death eventually results from hemorrhage, pulmonary thrombosis, bronchial pneumonia or cardiac insufficiency. Descent to sea level is accompanied by complete alleviation of symptoms and in the patients followed to date cure has been permanent at this elevation.

The analytic methods used in this study have been described previously.^{7,8} In most instances arterial blood was drawn in the morning before the day's work had begun. The results are given in the table. The medical history and physical examination of each of the healthy residents at 17,500 feet are given below.

Control Subjects. No. 1, Ca., a single man, aged 32, was examined July 11, 1935. He was born in the lowlands of southern Chile and came up to 17,500 feet 6 years before examination. On arrival he had headache and loss of appetite for 3 days. He had no symptoms of mountain sickness after that. His past history was essentially negative. He worked about 7 hours a day at 19,000 feet and was reputed to be one of the best and hardest workers at this altitude. He spent about 1 week a year at sea level.

Physical Examination. Pulse, 64; respiratory rate, 14; blood pressure, 112/78. His general appearance was healthy. There was dusky cyanosis over the exposed parts of the body. The chest was emphysematous in contour. The left border of the heart was 2 cm. inside the nipple line. No murmurs were heard. The pulmonic second sound was equal in intensity to the aortic second. The diaphragm on either side was elevated on percussion and descended slightly on deep inspiration. No râles were heard in the lungs. The liver and spleen were not palpable. The knee jerks were hyperactive. There was slight clubbing of the fingers.

No. 2, Tr., a single man, aged 29, was examined July 12, 1935. He was born in the lowlands of southern Chile and came up to 17,500 feet 9 years before examination. His past history was essentially negative. On arrival he had headache for 2 days. There were no symptoms of mountain sickness after that. His appetite was good and he felt as well as when he was at sea level.

Physical Examination. Pulse, 72; respiratory rate, 18; blood pressure, 108/98. There was dusky cyanosis over the exposed parts of the body. The eye grounds showed some dilatation of the veins but were otherwise normal. The chest was emphysematous in contour. The heart was not enlarged to percussion. The pulmonic second sound was reduplicated and louder than the aortic second. No murmurs were heard. The breathing was abdominal in type. The breath sounds were distant, but no râles were heard. The liver and spleen were not palpable. The knee jerks were hyperactive. There was slight clubbing of the fingers.

No. 3, Al., a married man, aged 39, was examined July 4, 1935. He was born in the lowlands of Bolivia and came up to 17,500 feet 14 years before examination. On arrival he had headache and dizziness for 5 days. There were no symptoms of mountain sickness after that. His past history was essentially negative. He worked 6 hours a day at 19,000 feet, slept well at night and felt as fit as when he was at sea level. He had 4 living children.

Physical Examination. Pulse, 44; respiratory rate, 16; blood pressure, 118/74. There was dusky cyanosis over the exposed parts of the body.

The eye grounds showed some dilatation of the veins. The chest was emphysematous in contour. The heart was not enlarged to percussion, the rate was regular and no murmurs were heard. The pulmonic second sound was equal in intensity to the aortic second. No râles were heard in the lungs. No abdominal organs were palpable. The deep reflexes were present. There was clubbing of the fingers.

No. 4, Fr., a single man, aged 35, was examined July 4, 1935. He was born in the lowlands of southern Chile and had not lived in the mountains until 2 years before examination. On arrival at 17,500 feet he had headache and loss of appetite for 4 days. He denied any symptoms after that. His past history was essentially negative. His appetite was good and he felt as well as when he was at sea level.

Physical Examination. Pulse, 62; respiratory rate, 22; blood pressure, 182/108. There was dusky cyanosis over the exposed parts of the body. The eye grounds showed slight dilatation of the veins. The heart was not enlarged to percussion, the rate was regular and no murmurs were heard. The pulmonic second sound was greater than the aortic second. No râles were heard in the lungs. The liver and spleen were not palpable. The deep reflexes were present. There was no clubbing of the fingers.

No. 5, Ba., a single man, aged 28, was examined July 12, 1935. He was born in the lowlands of southern Chile and came up to 17,500 feet 10 years before examination. After arrival he had headache for 3 days. He denied any symptoms of mountain sickness after that time. His past history was essentially negative. There was a loss of weight of about 10 pounds during the years after arrival. He worked 6 hours a day at 19,000 feet, slept well at night and felt as fit as when he was at sea level.

Physical Examination. Pulse, 68; respiratory rate, 16; blood pressure, 142/98. There was dusky cyanosis over the exposed parts of the body. The chest was emphysematous in contour. The heart was not enlarged to percussion, the rate was regular and no murmurs were heard. There was a reduplication of the pulmonic second sound which was greater than the aortic second. No râles were heard in the lungs. No abdominal organs were palpable. The deep reflexes were present. There was slight clubbing of the fingers.

No. 6, He., a married man, aged 36, was examined July 11, 1935. He was born in the lowlands of southern Chile and came up to 17,500 feet 7 years before examination. On his arrival he had headache and insomnia. He denied any symptoms of mountain sickness after the first 4 days. His past history was essentially negative. His appetite was good and he felt as well as when he was at sea level.

Physical Examination. Pulse, 76; respiratory rate, 19; blood pressure, 108/88. There was dusky cyanosis over the exposed parts of the body. The eye grounds showed some dilatation of the veins. The chest was emphysematous in contour. The heart was not enlarged to percussion, the rate was regular and no murmurs were heard. The pulmonic second sound was equal to the aortic second. No râles were heard in the lungs. The liver and spleen were not palpable. The deep reflexes were present. There was slight clubbing of the fingers.

COMMENT. The duration of residence (2 to 14 years) of the 6 healthy workmen at 17,500 feet is sufficient to allow us to consider them permanent inhabitants. Proceeding from this premise the characteristic changes in the constituents of the blood and in the medical examinations are assumed to be related to the effects of high altitude. The unanimous admission of symptoms of acute mountain sickness in the first days after arrival at this altitude

suggests that their occurrence is no indication of the ability to become acclimatized to elevations as high as 17,500 feet. In all subjects the neck was palpated to detect any enlargement of the thyroid. Colloid goiter and hyperthyroidism are not unusual in residents above 14,000 feet, but were not observed in any of the workmen. Other significant points in the physical examinations were normal blood pressure, a normal respiratory rate at rest, an emphysematous-like contour to the chest and clubbing of the fingers. In no subject were râles heard at the lung bases or was the liver or spleen palpable. In 3 subjects the pulmonic second sound was accentuated and greater than the aortic second sound. The average pulse rate for the 6 men at rest was 64. In Subject 3 the pulse rate was 44 at rest. This was not associated with cardiac arrhythmia or other evidence of heart block. The absence of tachycardia at high altitude suggests that the tachycardia of cardiac decompensation is not directly related to anoxemia. The emphysematous-like contour of the chest observed in most dwellers at high altitude is associated with an increased vital capacity.⁹ This is in contrast to pulmonary emphysema seen at sea level which is associated usually with a diminished vital capacity. In both conditions the alveolar sacs are dilated but in pulmonary emphysema the alveolar capillaries are partially obliterated while in emphysema at high altitude the alveolar capillaries are dilated.

The data obtained from the *examination of the arterial blood* show among other changes a large increase in the oxygen capacity, cell volume and red cell count. In 4 of the 6 subjects the oxygen capacity of the blood was above 30 vol. % and the cell volume above 72%. The highest cell volume observed was 81.8%. In this patient the blood was exceedingly viscous and it was drawn through a 19-gauge needle into an oiled syringe with great difficulty. The lowest saturation of arterial blood observed was 67.6%, the highest was 84.6% and the average for the 6 men was 75%. In 10 temporary residents at the same time of year at this altitude the average saturation was 76.2%.¹⁰ The absence of any difference between the arterial saturation in the temporary and the permanent residents suggests that permanent acclimatization is not associated with any significant change in this function of the blood. It may be assumed that an ascent to a given altitude is accompanied by a decreased oxygen saturation which remains relatively constant at rest as long as the subject remains at the same altitude. It is interesting that Subject 5, for example, had lived more than ten years at 17,500 feet with an arterial oxygen saturation presumably about 70% with no other symptom than increased dyspnea on exertion. The data for concentration of hemoglobin in cells, a coefficient derived from the oxygen capacity of the blood and the cell volume and expressed in volumes per cent of oxygen combining capacity per liter of cells, are given in the table.

The average range for normal men at sea level is from 44 to 46 vol. % per liter of cells. The average for the 6 subjects was 44.0. In the blood at sea level of patients with erythremia (polycythemia vera) the concentration of hemoglobin in the cells may be 25% below this amount.⁷

TABLE 1.—EXPERIMENTAL OBSERVATIONS ON ARTERIAL BLOOD.

Initials.	Oxygen capacity, vol. per cent.	Oxygen saturation, per cent.	Cell volume, per cent.	Cell hemoglobin, vol. per cent per liter.	Red blood cells, millions.	White blood cells.	Reticulocytes, per cent.	(Na) _s m.-Eq. per liter of serum.	(K) _s m.-Eq. per liter of serum.	(Ca) _s mg. per 100 cc. of serum.	(Protein) _s grams per liter of serum.	Total (CO) _s vol. per cent per 100 cc. of serum.	(Cl) _s m.-Eq. per liter of serum.
Healthy subjects examined at 17,500 feet.													
Ca.	32.7	74.8	74.7	43.4	7.48	5,200	0.6	6.20	38.1	108.3
Tr.*	32.5	72.8	44.2	7.54	4,600							
Al.	29.2	78.3	62.2	46.2	6.85	7,400	3.4	134.0	7.5	10.9	6.82	38.5	108.1
Fr.	24.6	84.6	52.2	46.7	6.15	8,300	0.4	7.1	10.1	6.47	30.3	115.0
Ba.	30.7	70.2	73.0	41.7	7.09	6,500	...	134.5	8.2	6.72	107.1
Hc.	34.2	67.6	81.8	41.4	9.10	5,000	30.8	104.9
Patient with chronic mountain sickness examined at 12,000 feet.													
T. V. de G.	25.0	71.4	55.0	45.0	7.37	5,400	2.2	135.9	4.1	9.7	7.63	47.4	106.1

* Venous blood.

The carbon dioxid content of arterial serum varied between 30 and 40 vol. % for the 6 men. The pH of the arterial serum reflected a mild degree of acidosis. These constituents have been discussed by Dill¹⁰ for the temporary residents and will not be considered here. The serum concentration of potassium and chlorid were normal or above normal and the concentrations of sodium were below normal. The concentrations of protein and calcium were within normal limits. These observations are few and the variations from normal are not large in most instances. There is an indication, however, that the summation of the acids and bases are from 1 to 3 m.—Eq. per liter below the average for persons at sea level. The results of the examinations of the urine, which included albumin, sugar and sediment, were negative.

It should be emphasized that the 6 subjects from whom these data were obtained were healthy workmen living at 17,500 feet, and accustomed to climb each day more than a thousand feet to an open sulphur mine where 6 to 8 hours of strenuous labor were performed 6 days a week. Employing these observations as controls, the pathologic syndrome infrequently observed following prolonged residence at high altitude will be considered.

Case of Chronic Mountain Sickness. T. V. de G., a 58-year-old widowed housewife, was seen June 10, 1935, complaining of severe hoarse-

ness. She was born in Oruro, Bolivia, 12,000 feet above sea level and had lived most of her life in high altitude. She had 6 siblings, 5 of whom were well; 1 sister had symptoms similar to those of the patient. As a young girl the patient was healthy. Her catamenia began at the age of 16 and ceased at the age of 50. She was married at 25 and had been pregnant about 10 times. She had 3 children living and well. The others had died in infancy with coughs and colds. In 1905, at the age of 28, she had a right-sided hemiplegia which lasted about 1 month but was followed by complete recovery. No further details were obtained regarding this episode. It occurred during her child-bearing years and possibly was related to one of her pregnancies. The absence of evidence of valvular heart disease when she was examined in 1935 suggests that the hemiplegia was not the result of an embolus from a heart chamber or valve. In 1931, she had an acute attack of cholelithiasis and jaundice. This was treated medically and there was no recurrence of symptoms. Her past history was otherwise negative except for symptoms associated with residence at high altitude.

At the age of 23 the patient went to live in Collahuasi, Chile, at an elevation of 15,400 feet. She lived in or near this town for the next 20 years. During the 15 years before examination she had lived at 12,000 feet, but frequently went up for short visits to 15,400 feet.

The present illness began when she was about 40 and living at 15,400 feet. At that time she had a difficult delivery at childbirth which was accompanied by an excessive hemorrhage. Shortly after this event, mild occipital headaches were noted which increased in severity up to the time of the examination. The occipital headaches at first were associated with tinnitus, a symptom not present in recent years. For over 10 years she had black spots before her eyes in the evening and infrequently colored scotomata. Vertigo was present when she stooped over. The mucous membranes of her mouth were usually dry and she had infrequent pain below her eyes which suggested to the examiner sinusitis. She had 1 to 3 sore throats a year.

The chief complaint was hoarseness. In recent years this had been very severe and in the winter months had been accompanied by aphonia which persisted for as long as 3 weeks. For many years she had a slight cough but there were never any night sweats or blood-tinged sputum. There were no cardiac symptoms until 1935 at which time she had mild non-radiating precordial pain accompanied by palpitation. She never had any edema of her ankles. In recent years she had followed a peculiar dietary régime. In the morning her appetite had been good and she had eaten her heaviest meal shortly after arising. By noon she had mild anorexia and by 3 o'clock she had lost her appetite. She had had no nocturia. In the 4 years previous to the examination she had tingling of her fingers and toes and numbness and cramps of her extremities at night. In summary, her presenting symptoms were occipital headache, spots before her eyes, hoarseness and aphonia, anorexia and tingling of her fingers and toes. When she went to a higher altitude several of the symptoms were aggravated and when she went to a lower altitude they were diminished. She had not gone down to sea level since 1920.

Physical Examination. Pulse, 78; respiratory rate, 20; blood pressure, 80/60 and 78/60. There was cyanosis of her lips and nails and a diffuse pigmentation over the exposed parts of her body. The conjunctivæ were suffused. The veins of the fundi were engorged but no exudates or hemorrhages were seen. The teeth were carious and the tonsils were large. The neck veins were full. The chest was barrel-shaped. There were occasional coarse râles at the lung bases which disappeared after coughing. The breath sounds over both sides of the chest were harsh. The breathing was upper thoracic in type. The heart was not enlarged to percussion. There was a

soft, non-transmitted systolic murmur at the apex. The pulmonic second sound was reduplicated and greater than the aortic second. The abdominal wall was relaxed. The liver and spleen were not felt. The knee jerks and ankle jerks were present and active. There was clubbing of the fingers and toes. There was no edema of the extremities. She appeared to be stable emotionally and was not suffering from a psychosis or neurosis.

Chronic mountain sickness is a little known entity in North America and no patients with this syndrome have been described in the United States. In addition to the 1 patient presented above, therefore, it seems desirable to include brief records of 2 of Monge's patients.¹¹ These patients were Peruvians and had acquired chronic mountain sickness in the Peruvian Andes.

Patient M. N., a married engineer, aged 38, was seen in 1923 complaining of pigmentation of his skin and a diminution in capacity for work. Born at sea level, he made his first climb to 11,500 feet in 1906. He had severe symptoms of acute mountain sickness at that time and was compelled to return to sea level after a few days. In 1909 he went to 14,000 feet and became acclimatized. On one occasion 2 years later he had transient paresthesias in his extremities and made several errors in a series of mathematical calculations. These disturbances disappeared in a few hours and returned about once a year during the next 2 years. In 1913, he went down to sea level because of the tingling in his extremities and was relieved shortly after the descent. Four months later he returned to 14,000 feet and worked satisfactorily for the next 8 years at this altitude. In 1922, he sought medical advice because of a purple face, congestion of his conjunctivæ and pharynx, vertigo and transient amblyopia. He returned to sea level and was promptly relieved.

Physical Examination. When seen in 1923 his skin was deeply pigmented and the mucous membranes were purple. The conjunctivæ were suffused. There was generalized dilatation of the superficial veins. The contour of the chest was not remarkable. The heart and lungs were normal.

Partial Laboratory Data. Venous blood. R. B. C., 8.80 million per c.mm. W. B. C., 10,000 per c.mm.; Wassermann reaction, negative; non-protein-nitrogen, 30 mg. per 100 cc. Urinalysis. Albumin, absent; sugar, absent; sediment, normal.

Course. In 1924, he was treated for pneumonia at sea level and made a satisfactory recovery. Sometime later he went up to 8,200 feet and lived there for the next 5 years without any inconvenience.

Patient M. L. B., a married laborer, aged 48, was seen in 1926 complaining of headache, dizziness and weakness. Born at sea level, he went up to 15,400 feet at the age of 12 where he lived and worked without symptoms until the age of 36. At that time he had shooting pain in his extremities which persisted for several months. He continued working for the next 4 years until he was compelled to go to bed because of the pain. At this time he thought that his purple color was deepening in intensity and he suffered from severe headache, vertigo and visual cloudiness. In 1924, he went down to 8,200 feet, remained there for several months and felt much better. When he returned to 15,400 feet all of his symptoms reappeared.

Physical Examination. When seen in 1926 the skin was deeply pigmented and the mucous membranes were purple. There was generalized vasodilatation. The conjunctivæ were suffused. The thorax was emphysematous in contour and the respiratory movements were limited. The heart was normal. The tip of the spleen was palpable. There was clubbing of the fingers.

Partial Laboratory Data. Venous blood. R. B. C., 8.90 million per c.mm.; W. B. C., 11,200 per c.mm. Urinalysis. Albumin, absent; sugar, absent; sediment, normal.

Course. As long as he remained at sea level his only symptom was weakness. In 1927, he ascended to 12,100 feet at which altitude he had headache, pains in his extremities and visual cloudiness. Shortly after that he went to 14,800 feet and was able to perform light work without discomfort. Four months later he had precordial pain, substernal oppression and abdominal distress. His headaches were very severe and he had marked asthenia. Late in 1927 he became stuporous and was taken down to sea level. On examination at that time he had pulmonary edema. At sea level recovery was prompt and he went to work at that elevation. In 1928 against advice he returned to the mountains and shortly after complained of headache and vertigo. That night he lapsed into coma and was taken down to sea level. His pulse was 80, his blood pressure 90/40 and his respiratory rate 20. He recovered in 48 hours and 1 week later went to work at sea level where he continued without symptoms during the years following.

COMMENT. Chronic mountain sickness may occur in either sex in the fourth, fifth or sixth decade of life. The onset of symptoms may be from 2 to 20 years after arrival in the highlands.¹² These symptoms include headache, hoarseness, anorexia, weakness and pains in the extremities. They are observed in persons previously in good health and presumably adequately acclimatized. The headache is occipital in location and does not radiate. It is unlike the headache of acute mountain sickness which is localized to the vertex and most severe. If the headache of chronic mountain sickness is accompanied by vertigo and spots before the eyes, chronic nephritis may be suspected. Hoarseness may be intermittently severe and frequently progresses to transient aphonia. A brassy, non-productive cough may accompany the laryngitis. Dyspnea on exertion may be the only cardiac complaint. Precordial pain, palpitation and tachycardia are observed during acute exacerbations only. The anorexia of chronic mountain sickness is unusual and characteristic. Following a night's rest the morning appetite is good and a substantial breakfast may be the largest meal of the day. After the patient is up and about the appetite diminishes and by noon no more than a light lunch is ingested. By mid-afternoon the anorexia may be complete and little or no food is taken during the remainder of the day. There may be alternate periods of constipation and diarrhea. There are no characteristic urinary complaints. Tingling, numbness and cramps of the extremities are observed frequently. In spite of the number and severity of the symptoms, most patients are ambulatory and during an acute crisis only are they stuporous or comatose.

On *physical examination* the dusky cyanosis and pigmentation of the exposed parts are similar to those observed in most residents at high altitude. The dilatation of the superficial veins and the suffusion of the conjunctivæ suggest erythremia. In the patient seen by us the veins of the fundi were dilated but no hemorrhages

or exudates were seen. Inspection of the mouth and throat shows no abnormality other than a thick tongue and prominent pharyngeal veins. The chest is emphysematous in contour, a characteristic of dwellers at high altitude. The diaphragmatic movements are decreased and breathing is usually abdominal or lower thoracic in type. During a remission the heart is not enlarged to percussion and there are no murmurs indicative of valvular heart disease or cardiac dilatation. The pulmonary second sound is louder than the aortic second and is reduplicated. Hypotension is usually observed and when accompanied by weakness and pigmentation of the skin, Addison's disease may be suspected. In Monge's series¹¹ splenomegaly and hepatomegaly were observed in only 10% of the patients. In patients in whom the spleen is enlarged this enlargement is slight and does not reach the size observed in patients with erythremia. There is usually clubbing of the fingers. In our patient no characteristic changes from the normal were observed in the neurologic examination.

The *laboratory data* are not unlike those obtained from asymptomatic subjects living in the mountains. The oxygen capacity at one examination in the patient T. V. de G. was 25.0 vol. %. The average for 10 temporary residents at the same altitude⁷ was 23.1 vol. %. The concentration of hemoglobin per liter of cells was unchanged from that observed in normals at sea level. The higher oxygen capacity of the blood of the control subjects living at 17,500 feet is related to the higher altitude at which they were studied. In chronic mountain sickness the red cell count may increase as the disease progresses but there is no direct correlation between the increased concentration of cells and the severity of the disease.¹² The amount of oxygen carried per cc. of arterial blood may be no greater than that carried at sea level but the oxygen tension is reduced. The carbon dioxide content of the arterial blood was above the concentration observed for the temporary residents at that altitude. The concentration of the other electrolytes in the serum showed nothing remarkable. The white cell count rarely exceeds 10,000 per c.mm. The results of the examination of the urine were negative.

The *differential diagnosis* between chronic mountain sickness and the diseases with which it may be confused must be broadly qualified. Chronic mountain sickness is a disease of high altitude and conditions similar to it are seen generally at or near sea level. Therefore, in the differential diagnosis chronic mountain sickness as observed above 10,000 feet will be compared with certain pathologic conditions as observed at sea level. It will be obvious that many of the diseases discussed are associated with severe disturbances of the cardiorespiratory system which prevent an afflicted person from going into regions of decreased oxygen tension. Such a condition is pulmonary endarteritis obliterans (Ayerza's disease).

In the terminal stage¹³ this may be accompanied by headache, dizziness, deep cyanosis, clubbed fingers, reduplication of the pulmonic second sound, emphysema and polycythemia. In excluding this disease, the altitude at which the patient is examined is important. It is doubtful if a person with a degree of pulmonary endarteritis severe enough to produce these symptoms could live above 10,000 feet. A differential point in the laboratory data is the carbon dioxide content of arterial blood. In blood from a patient with the latter disease an increased carbon dioxide content is observed, while the blood from a patient in the highlands with chronic mountain sickness has a diminished carbon dioxide content.

Congenital heart disease of the cyanotic type (*morbus caeruleus*), although infrequently seen, has many of the symptoms mentioned above in the several combinations. Again most patients with such a malady neither live to adulthood nor are they able to live above 10,000 feet and become acclimatized. The syndrome described by Fallot offers a possible exception to this statement. Persons with this condition may live longer than three decades¹⁴ and may ascend to altitudes of several thousand feet. With the latter condition disturbances of vision, headache, dizziness, paresthesias and hypotension are not unusual. The important differential details are the history, the physical examination of the heart and the electrocardiogram, which in most cases of the *morbus caeruleus* shows marked right axis deviation.

Acquired heart disease is easier to exclude. A history of rheumatic fever in young people, syphilis in patients in the middle decades and symptoms of hypertensive or arteriosclerotic heart disease in the older age groups are useful. A deep cyanosis is observed infrequently in acquired heart disease except with a failing heart while cyanosis is characteristic of chronic mountain sickness without decompensation.

Chronic nephritis may be suspected when a patient has headache, spots before the eyes, anorexia and weakness. The hypotension, absence of anemia and edema, and the presence of cyanosis with the normal urinary findings are helpful in excluding this condition.

The greatest opportunity for confusion exists when erythremia (polycythemia vera) is suspected. This is especially so if one compares the latter as observed at sea level with chronic mountain sickness as observed above 12,000 feet. But even with this qualification the two diseases may be distinguished readily. In erythremia hypotension is rarely observed and more than 50% of the patients have hypertension.¹⁵ Splenomegaly and hepatomegaly are found in a large percentage of patients with erythremia¹⁶ and in a minority of patients with chronic mountain sickness. Laboratory studies are of further aid. At sea level erythremia is not accompanied by decreased saturation of arterial blood,^{17,18} although the appearance of the patient suggests the presence of cyanosis. Many patients

with this condition have either a leukocytosis or a leukemic blood picture.¹⁹ A normal concentration of white blood cells is found in patients with chronic mountain sickness. These conditions may be further differentiated by their response to increased oxygen pressure. Patients with erythremia have shown neither symptomatic improvement nor a decreased oxygen capacity of the blood following oxygen therapy for as long a period as 2 weeks.²⁰ On the other hand prompt alleviation of symptoms following descent to a lower altitude is characteristic of chronic mountain sickness. Accompanying this improvement there is a decrease in the red cell count and the oxygen capacity of the blood. The depth of the descent necessary to cause improvement is a function of the severity of the disease. In patients with mild symptoms alleviation may follow a descent of only a few thousand feet while in others it is necessary to go down to sea level for relief.

The *pathogenesis* of chronic mountain sickness is not known. The high concentration of circulating hemoglobin in these patients attracts one's interest but this is probably a physiological response. All of the normal subjects discussed in this study had an increased concentration of red blood cells and an elevation of the oxygen capacity of the blood but did not have symptoms which are thought to be pathognomonic of this disease. It is significant that 3 of the workmen lived for more than 12 years above 17,000 feet with an oxygen capacity of the blood presumably above 29 vol. %. The frequent occurrence of an increase in hemoglobin in the blood of residents at high altitude suggests that this increase *per se* is not responsible for the symptoms infrequently observed. Associated with the increase in hemoglobin is the decreased saturation of arterial blood. We can assume with moderate certainty that individuals may live for more than 10 years with an arterial saturation of oxygen below 80% meanwhile enjoying good health. Beyond this we have little information. It is possible that 20 or 30 years of an unsaturation of arterial blood of this degree may produce pathologic changes in the body. There is little evidence that anyone is immune to chronic mountain sickness provided he lives at a sufficiently high altitude for a sufficiently long time. The general effect of prolonged anoxemia upon a healthy individual at sea level is not known. The effect of prolonged anoxemia upon the concentration of hemoglobin per liter of cells in a patient with congenital heart disease is worth noting. Hitzenger²¹ reported an oxygen capacity of the blood of 35.2 vol. % and a cell volume of 75% in a 26-year-old patient who had been cyanotic from birth. The oxygen saturation of the arterial blood was 62%. The absolute increase in circulating hemoglobin with a normal concentration of hemoglobin per liter of cells is a response similar to that observed at high altitude. The calculated oxygen tension in the tissues in this patient was 30 mm. Hg., approximately half that observed in a normal control.

As an explanation of the pathogenesis of chronic mountain sickness Monge has stressed the fact that there may be a low coefficient of diffusion of oxygen in the lungs of affected persons. Harrop²² observed that in acute mountain sickness a low coefficient was characteristic. Whether or not, a similar phenomenon may be observed in chronic mountain sickness is not known. If this were the correct explanation it would account for the varying susceptibility of individuals. It fails, however, to account for the long interval between arrival in the mountains and the onset of symptoms and for the prompt relief afforded by a descent of a few thousand feet.

The dilatation of the veins of the pharynx and the stomach are responsible probably for the symptoms of hoarseness and anorexia respectively. The hypotension is presumably a function of the generalized vasodilatation.

Another biologic factor which may exert an influence at high altitude is radiation. The peculiarity of its effect proceeds essentially from the abundance of ultra-violet rays. The known effect of these rays on the skin are erythema, pigmentation and inflammation. It is possible that prolonged exposure exerts a pathologic effect on the internal organs as well.

The *treatment* of chronic mountain sickness is the descent to a lower altitude. Acute exacerbations may be relieved temporarily by oxygen inhalation. When permanent residence is taken up at a lower altitude symptoms are alleviated for months or years. At sea level the cure is presumably permanent. Monge observed 1 patient without symptoms during a 10-year period at sea level.

Conclusions. The justification for presenting the syndrome of chronic mountain sickness as a disease entity is twofold. The environment, symptomatology, physical examination and laboratory data are distinct and in their totality are unlike any other disease. Secondly, the syndrome represents more than the physiologic response to high altitude. The disease is associated with prolonged anoxemia but the rôle that this plays in the pathogenesis is uncertain. A low coefficient of diffusion of oxygen has been proposed as the etiologic agent but this is not proven. The disease is similar in many respects to erythremia but certain fundamental differences have been pointed out. Chronic mountain sickness is a progressive disease which manifests a remarkable recovery under increased oxygen pressure.

We are grateful to Dr. P. D. White for many helpful suggestions in the preparation of the manuscript.

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THEVETIN IN THYROTOXICOSIS.

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TACHYCARDIA is one of the cardinal signs of hyperthyroidism. The pulse rate in these cases remains fast even in hours of sleep,¹ and the acceleration appears to correlate with the elevation of metabolic rate.² Digitalis is useless in thyrotoxic tachycardia unless there is an accompaniment of cardiac failure.^{3,4,5} Iodin preparations such as Lugol's solution often reduce both the metabolic and the pulse rates,⁶ but occasionally the lowering of the metabolic rate is not coupled with a decrease in pulse rate. The persistent fast rate thus constitutes a surgical risk which cannot be readily minim-

ized. In their first clinical report, Arnold, Middleton, and Chen⁷ included the results with thevetin in a case of thyrotoxic heart disease. The new cardiac drug, given by mouth, adequately controlled the signs of decompensation. In view of the fact that a physiologic unit of thevetin appears to be more efficient than an equivalent unit of digitalis in slowing the pulse rate,⁸ it was thought it might be of interest to try it in thyrotoxicosis with the chief aim of reducing the pulse rate.

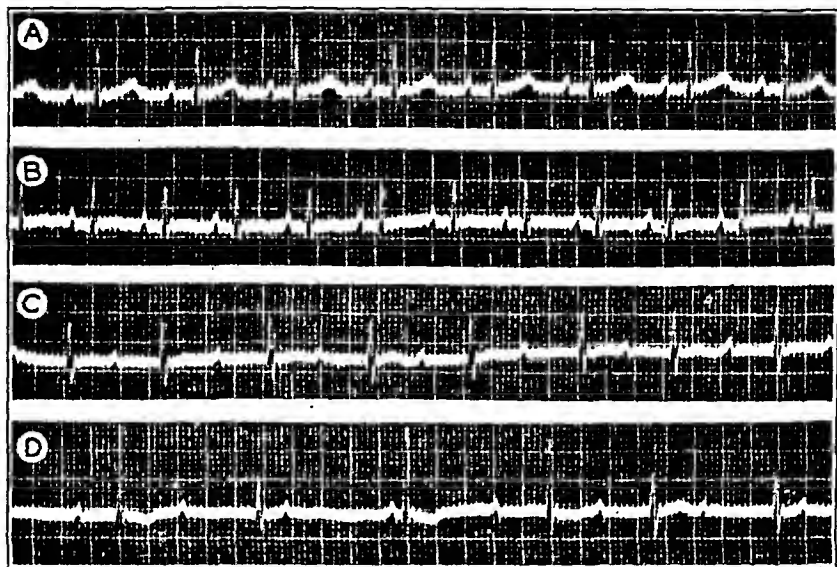


FIG. 1.—*Action of Thevetin in Experimental Hyperthyroidism.* Cat 1388, male, weight 2.898 kg., was given by mouth 5 doses of desiccated thyroid gland, U. S. P., 60 mg. per kg. in a week's time. A 1 to 20,000 solution of thevetin was then injected intravenously at the rate of 1 cc. per minute. Electrocardiograms were taken from Lead II under ether anesthesia, before and after the thyroid medication and during the injection of thevetin. A, Normal electrocardiogram. Sinus rate, 173 per minute; P-R 0.09 second. B, Electrocardiogram after thyroid therapy. Sinus rate, 240 per minute, an increase of 67 beats over the normal. P-R 0.08 second. C, Electrocardiogram after 0.44 mg. of thevetin per kg. had been injected. Sinus rate, 168 per minute, a decrease of 72 beats. P-R was prolonged to 0.19 second. D, Electrocardiogram after 0.47 mg. of thevetin per kg. had been administered. Notice the premature beats. Auricular rate, 165 per minute; ventricular rate irregular, approximately 120 per minute, a reduction of 50%.

Before this point was put to test clinically, experiments were carried out in cats in which hyperthyroidism was induced by feeding desiccated thyroid gland. When tachycardia became significant, thevetin was slowly injected under ether anesthesia. An example of the results is given in Fig. 1. It should be noted that thevetin effectively produced a diminution of the heart rate.

A series of 22 consecutive cases of hyperthyroidism was then studied with thevetin. As shown in Table 1, 16 patients were

TABLE 1.—THE EFFECT OF THEVETIN ON THE PULSE RATE IN THYROTOXICOSIS.

Case No.	Sex.	Age.	Pulse at first visit, per min.	Thevetin therapy.		Average pulse rate.		
				Time (relative to operation).	Dose, cat units.	Before thevetin, per min.	After thevetin, per min.	At the time of discharge, per min.
1	M	23	100	Immediately before	9	120	85	72
2	M	57	120-130	Immediately before	3	110	98	72-80
3	F	39	120	Immediately before	3	120	90-100	80
4	F	25	100	After	3	120	82-88	Below 100
5	F	25	120	Before	4.5	120	94	80
6	F	23	120	Immediately before	3	100	80	70-86
7	F	56	96	Immediately before	3	130	100	Below 90
8	F	32	120	Before	3 every other day	120	Below 100	76
9	M	25	110-120	Immediately before	3	124-132	120-130	70-80
10	F	30	140	Before	3	108	86	110-100
				Immediately before	3	140	94	
11	M	53	100	After	3	130	108	90 or below 80
				Immediately before	6	112	88	
12	F	34	104	After	3	124	90-100	80
				Immediately before	3	104	90-100	
13	F	35	140	Immediately before	6	132	72-108	
14	F	37	108	After	3	100	62-92	80
				Immediately before	6	120	80	80-100
15	F	60	88	After	3	120	110	
16	F	54	150	After	3	110	72-80	72-80
				Immediately before	6	150	150	*
17	F	45	120	Immediately before	3	100	132	
18	F	25	120	After	6	160	90-130	80
				After	3	120-130	100 or less	†
19	F	35	105	Before	3 semiweekly for 6 wks.	120	100-110	80-86
20	F	38	120	Immediately before	3 every 4 hrs.	120	100	Below 100
21	M	22	120	Immediately before	3	104	112-114	72-80
22	M	35	80?	After	3	112	96	96

* The patient died 6 days after operation.

† Treated at home.

female, and 6 male. Their ages ranged from 22 to 60. The financial status of the majority of the patients was such that only a short period of hospitalization was permitted. As a rule, they were advised to go to bed as soon as the diagnosis was established. Lugol's solution was administered in the dosage of 10 to 15 drops 3 times a day. They remained in bed for 1 to 2 weeks or longer, until they were cautiously transferred to the hospital. Metabolic rate was measured in a few patients who could easily stand the strain, but omitted in others who were comparatively more irritable. In every case, thyroidectomy was performed 1 to 12, on the average 4, days after admission. With the exception of 2, 20 patients were discharged from the hospital 6 to 11 days after the operation. Thevetin was injected by vein usually immediately before the incision, but occasionally during the pre-operative or postoperative stages. The pulse rate was counted frequently, both before and after the injections. The oral route of administering thevetin was tried in a few cases but was abandoned on account of its absence of response in the amounts employed.

The results in Table 1 indicate that in 18 cases thevetin caused a definite drop of pulse rate, varying from 10 to 52 per minute. This diminution, which appeared a few minutes after the injection, was particularly gratifying to the surgeon and the anesthetist during the operation, for in several patients prolonged anesthesia, extensive manipulation, and considerable loss of blood did not bring about an acceleration of the heart rate. The pulse reduction persisted in half of the cases, but in the other half, there was a return of tachycardia several hours after the operation. Repetition of thevetin therapy in the latter, however, assisted in restoring a rate well below the arbitrarily chosen limit of 100. The administration of thevetin in the pre-operative stage was also followed by a drop in the heart rate, but tachycardia often began to return 5 to 6 hours after the injection, so that repeated doses were necessary in order to subdue the cardiac activity continuously. The most beneficial effect of thevetin was undoubtedly obtained during thyroidectomy by reducing the surgical risk of cardiac mishap. The reduction in heart rate with 6 to 9 cat units of thevetin was relatively greater than that with 3 cat units, although occasional extrasystoles were observed with the larger doses. No accumulative effect had been noted from even larger doses.

For illustration of the successive use of thevetin the following case may be briefly cited:

CASE 13.—Mrs. D., aged 35, complained of nervousness and restlessness. Her family and past history was unimportant. On examination on June 6, 1935, she showed fine tremor of hands, exophthalmos, and moderate enlargement of the thyroid gland. Her pulse was 140 per minute. The diagnosis of exophthalmic goiter was obvious. She was advised to go to bed at once and remain there. Lugol's solution was prescribed, 15 drops 3

times a day. On June 18, 1935, she was admitted to St. Vincent Hospital, at which time her pulse rate was the same, that is, 140 per minute. On June 22, 1935, the patient was taken quietly to the operating room. Her pulse rate then was 132 per minute. Following an intravenous injection of 6 cat units of thevetin, it dropped to 108. Under ethylene anesthesia, the right lobe, isthmus, and part of the left lobe of the thyroid gland were removed. There was a gradual reduction in the heart rate. It was 80 per minute 3 hours, and 72 per minute 6 hours, after the operation. At the end of 24 hours, it rose to 100, but upon the administration of 3 cat units of thevetin, it fell to 92. Twelve hours later, an additional dose of thevetin was injected. Forty-eight hours after the operation, the pulse rate was found to be 62 with occasional extrasystoles. No more thevetin was given. The patient was discharged on June 28, 1935, with a pulse rate within 80 per minute. One month after the operation, her pulse rate was 100 per minute; 7 months after, it was found to be 80 per minute. Her nervous symptoms and exophthalmos had completely disappeared, and she had gained 10 pounds in weight.

One patient (Case 8) had symptoms and signs of heart failure, such as, edema, dyspnea, etc. The administration of thevetin promptly brought about relief during the pre-operative period. The high efficacy of thevetin as a cardiac drug should be specially indicated in hyperthyroidism with myocardial damage. Similarly, it should be tried in auricular fibrillation complicating thyrotoxicosis.

The response of 2 cases (Nos. 9 and 16) to conservative doses of thevetin was very slight or *nil* during the operation, 1 of which (Case 16) was in a highly toxic state, the pulse rate ran constantly at 150 per minute. This patient died of postoperative crisis. In 2 other cases (Nos. 17 and 21) thevetin failed to forestall the acceleration of heart rate at operation, although a dose of 6 cat units in 1 case (No. 17) produced a drop of pulse rate postoperatively.

Summary. Thevetin injected intravenously in the dosage of 3 to 9 cat units, successfully diminished the heart rate in 18 out of 22 cases of thyrotoxicosis, but failed in the remaining 4.

The drug is most useful during the operation for the reduction of surgical risk by subduing the operative cardiac hyperactivity, and it is also helpful during the pre- and postoperative stages in lowering the pulse rate temporarily as desired. Consequently, hospitalization can be satisfactorily shortened by the elimination or reduction of tachycardia during pre- and postoperative stages.

In the presence of cardiac failure accompanying hyperthyroidism, the administration of thevetin is an important pre-operative measure and for postoperative safety.

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NOTE ON THE USE OF EVIPAL (N-METHYLCYCLOHEXENYL-METHYL BARBITURIC ACID) IN CORONARY OCCLUSION.

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It is the consensus of intelligent medical opinion that relief from pain and absolute rest are essential in treating coronary occlusion; that somnolence for the first 24 to 48 hours or more after an acute closure is very desirable to eliminate the anxiety accompanying the severe precordial and arm pain. It is for patients who have not been relieved by the vasodilators (nitroglycerin, amyl nitrite, aminophyllin); the common narcotics (morphin, dilaudid, pantopon, codein); or the use of caffein sodiobenzoate and phlebotomy; that I wish to recommend the use of Evipal. In the case described below I am convinced that death would have ensued without it.

Case Report. A. S., aged 71, white male, with a completely negative previous history, awakened on February 8, 1936, with moderate precordial pain radiating to the left shoulder and to the back of the left arm. This pain gradually increased in severity so that medical attendance was sought. Nitroglycerin under the tongue immediately gave some relief but complete relief was obtained only after morphin (gr. $\frac{1}{4}$) was given. Physical examination was negative, except for a temperature of 100 and a pulse of 96. Blood pressure was 150/90. Convalescence was uneventful until 36 hours later. During this interval the patient was receiving luminal and aminophyllin and remained absolutely in bed. At the end of 36 hours the pain returned with excruciating severity. The radiation was the same. Nitroglycerin and amyl nitrite were given without relief. Morphin sulphate (gr. $\frac{1}{2}$) was given and repeated in 20 minutes when patient began thrashing about in bed because of the severity of the pain. He became quite cyanotic. The pulse rose to 140 and lost some of its volume. His anxiety and fear of death were overwhelming. A phlebotomy of 300 cc. gave no improvement. Evipal 10% was started intravenously. After 1 cc. the patient was drowsy; after 2 cc. he was asleep; 4 cc. were given in all. He remained asleep for 15 minutes with easy regular breathing. On awakening he had only a dull precordial ache. The severe pain and overwrought anxiety were gone. He was then kept somnolent with the usual sedatives. A definite pericardial friction rub appeared 12 hours later, confirming the diagnosis. He is making an uneventful convalescence.

Evipal is described by its manufacturers, the Winthrop Chemical Company, as an "intravenous anesthetic." It is supplied as a powder in ampules of 0.5 gm. and 1 gm., and is prepared shortly before use by the addition of distilled water to make a 10% solution.

ATABRINE PIGMENTATION.

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THE antimalarial drug atabrine (atebrin) has been used with very favorable results both in this country^{8,9} and abroad.¹⁻⁷ The increasing popularity of the drug however, because of a secondary effect, namely, yellow pigmentation of the skin, has introduced a new and confusing factor into the differential diagnosis of conditions that are characterized by skin color changes. Frequently a patient who has been treated for malaria develops, or still suffers, from some other condition for which he consults a physician several weeks later. A yellow discoloration of the skin may be present, and, not aware of the possibility of atabrine pigmentation, the physician may believe that he is dealing with, usually, jaundice. The existence of postmalarial cirrhosis is doubtful and the hypertrophic malarial hepatitis that may occur in long-standing cases causes no characteristic clinical symptoms.^{10,11} During the course of malaria a hematogenous and perhaps a hepatogenous discoloration of the skin may occur in the hemoglobinuric form of the disease, but a yellow skin cannot ordinarily be regarded as a malarial sequela. Some other explanation for postmalarial skin discoloration must be sought, either in a disease process that is unrelated to malaria, or to the deposition of a dye. It is our purpose to describe the temporary skin discoloration of atabrine, and the means of avoiding diagnostic errors with regard to its recognition.

Atabrine is an acridin dye derivative,¹² chemically related to plasmochin and to acriflavin. It is administered by mouth in yellow tablets of 0.1 gm. each, 3 times daily for 5 days, although it is occasionally given intravenously. A new soluble compound, atabrine musonate,¹³ has recently been introduced and is said to be rapidly effective in small doses given intramuscularly. Parenteral administration, however, does not eliminate the possibility of pigmentation.

The yellow discoloration of the skin by atabrine is diffuse and most prominent on the dorsum of the arms, hands, and feet. It is also clearly seen on the forehead and face, and may form a golden ring around the mouth. It is accentuated in the interdigital skin folds, neck creases, under the breasts, etc. The palate may seem to show pigmentation at times but is unreliable as a diagnostic index. The rest of the skin is but slightly affected. The hue varies with the intensity of the pigmentation and with the basic color of the patient's skin. It may be greenish, lemon, or golden-yellow, but in any case

a strong yellow component is clearly evident. There is no dermatitis or change in the texture of the skin. Contrary to descriptions given by other observers,^{2,14,15} we have failed to see any significant degree of discoloration in the scleræ; in fact, we have found this a useful point in distinguishing the condition from jaundice.

In a person who is pale to start with, one might at first glance suspect pernicious anemia. In a darker skin, the pigmentation may give the impression of mild jaundice. The yellow pigmentation of carotinemia may be a source of confusion since here too the scleræ are generally not stained, but the dermal pigmentation affects the ventral surfaces of the hands and feet most characteristically. Other conditions that may be thought of are Addison's disease, subacute bacterial endocarditis, yellow fever, or pigmentation from picric acid as occurs in TNT workers.

Some patients remember having had nausea or lower abdominal cramps early in the course of the treatment. In others the cramps may not appear until 2 or more weeks after the treatment is over, and in fact, may be the presenting symptom on hospital admission.^{1,4,15} In cases of vague lower abdominal pain not otherwise explained, the solution may lie in the knowledge that atabrine had been taken some weeks before, even though no pigmentation persists, or, as in negroes, where pigmentation cannot be detected.

There can be no doubt that the pigmentation is due to deposition of the dye in the skin, and not to a secondary metabolic disturbance. Working with laboratory animals, Hecht¹⁶ found by fluorescence exhibited under ultraviolet light that the dye appeared in the skin 36 hours after peroral administration. Various observers^{17,18,19} have reported impairment of liver function in the majority of untreated malarial patients. There is no evidence that such impairment is enhanced by atabrine. Ruge,¹⁸ in fact, has shown that chemical and liver function tests which point to hepatic damage in acute malaria return to normal under atabrine treatment. DeLangen and Storm²⁰ have compared quinin, plasmochin and atabrine and point out that plasmochin, which does not cause pigmentation, very often causes hepatic damage, that quinin never does, and that atabrine does so only rarely and then in cases of malnutrition where the liver is poorly fortified with glycogen.

Factors which have been thought to be contributory causes of pigmentation, especially when it is prolonged, are renal insufficiency,^{5,19} constipation, influenza, exhaustion associated with intercurrent infection, and anemia.²¹ Hecht¹⁶ has demonstrated that after ingestion the dye is absorbed in the small intestine and that much is passed back with the bile to the bowel where some reabsorption takes place. Tropp and Weisc have shown that excretion, which is very slow at best, is divided about equally between urine and stool. It is conceivable that in constipation a greater than usual reabsorption of the dye takes place, and hence more becomes

available for deposition in peripheral areas. We are inclined to believe that anemia plays a rôle. In 2 cases, when the hemoglobin content was considerably raised, either by transfusions or hematinics, the excretion of atabrine in the urine increased very noticeably. Although blood studies thus far, by Hecht,¹⁶ and by us, have failed to show satisfactorily how atabrine is partitioned between cells and plasma, we suspect that the drug is carried in or on the red blood cells, as is thought to be the case with quinin. When there is a paucity of cells available for such transfer, the dye remains for a longer time in the various depots, among which is the skin.

Pigmentation following the use of atabrine is to be expected in many of the cases treated, especially when excretion of the dye does not begin within 3 days after the first dose. This, however, is said to vanish in not more than 2 or 3 weeks^{1,4,14} although urinary excretion continues for from 4 to 10 weeks as a rule. No reports of cases with prolonged pigmentation have come to our notice except the recent paper by Soni,²¹ in which 2 cases are reported from India. The pigmentation lasted a month in 1 instance and about 3 months in the other.

During the past 5 months we have had the opportunity of seeing 8 instances of prolonged atabrine pigmentation. These were admitted with complaints unrelated to malaria, but they incidentally presented a yellow pigmentation of the skin the significance of which was not appreciated by the attending physicians until it was ascertained that the patient had been treated for malaria some weeks before. Four cases showed the discoloration 6 weeks after the final dose, one 8 weeks, one 16 weeks, and two 18 weeks after the last tablet was taken. One patient, however, took 3 courses of atabrine in the space of 2 months on her own initiative. We saw another patient 1 week after the last dose of a second course which was taken 5 weeks after the first. This patient showed only very minimal pigmentation on the dorsum of the hands and feet.

Diagnosis. If it is elicited that three somewhat bitter, yellow tablets were taken each day for 5 days for malaria, it is very likely that those tablets were atabrine. Plasmochin tablets are also yellow but are not bitter, and they are usually given with or after a quinin course for a period of longer than 5 days. There is nothing particularly distinctive or constant about the pigmentation itself that makes it proof against confusion with other causes of discoloration. The distribution and range of shade described above may be said to be suggestive of atabrine pigmentation but scarcely more than that is warranted. Tests for hyperbilirubinemia should, of course, be carried out to avoid confusing those cases in which jaundice and atabrine pigmentation may appear concurrently. Atabrine causes no spectroscopic changes in the blood, nor does it have its own characteristic absorption bands in the visible spectrum.

The tests for atabrine in the urine are simple, quick, and quite

reliable. A physician having access to the ordinary laboratory equipment should be able to detect atabrine even if only 0.02 mg. is present in the urine. The following is a procedure which we have modified in several respects from Tropp and Weise.²²

Test. One hundred cc. of urine in a separatory funnel is made strongly alkaline with 10 to 15 cc. of 30% sodium hydroxide. Add 50 cc. of ether and shake for $\frac{1}{2}$ minute. On standing, the ether rises to the top. If the presence of a gelatinous material prevents a clear line of separation, allow most of the urine to run off, add 4 to 5 cc. of 95% alcohol, and shake again for a few seconds. Run the underlying urine layer off. Wash the ether extract by adding 50 cc. of water slightly alkalized with sodium hydroxide and shaking. After separation of the layers, the wash water is run off. Now add 5 cc. of 10% hydrochloric acid to the remaining ether extract, shake for $\frac{1}{2}$ minute and after separation of the layers, run the acid extract (lower layer) into a small narrow test tube. If the concentration of atabrine is high, the acid extract will appear green in ordinary light. If it seems colorless, examine the tube in a dark room against a black background in a beam of very strong light coming from the side. A green fluorescence indicates atabrine. If no such light is available, the tube may be viewed in the dark, from the side, with a strong light, as from a good pocket light or electric battery otoscope, illuminating it from below. On moving the light from side to side underneath the tube, a vertical or oblique beam of green fluorescence will be seen. In order to prevent dispersion of light from dust particles on the outside of the tube which might prevent a small degree of fluorescence from being visible, dip the tube into amyl alcohol, mineral oil, or liquid of similar consistency before examining for fluorescence. In the absence of a separatory funnel, an 8-ounce stoppered bottle may be used. Separation of the layers can then be most completely effected by transferring the mixture to a tall narrow cylinder from which the upper layer may be poured.

We have found that acriflavin in the urine can be detected in extremely small amounts by this procedure, but in contrast to the somewhat bluish-green fluorescence of atabrine, acriflavin has a yellow-green fluorescence. This exception to the specificity of the test for atabrine is not of practical importance, however, for acriflavin is completely excreted in the course of a few days.

The use of hydrochloric acid for extraction of the atabrine from the ether instead of the sulphuric acid recommended by Tropp and Weise, avoids the possibility of confusion due to the presence of quinin, quinidin, or even plasmochin, which in any but halogen acids give a royal blue fluorescence that can overshadow the green of atabrine. No confusion results from the presence in the urine of the coal tar derivatives, barbiturates, iron compounds, digitalis, strychnin, the opium alkaloids, phenolphthalein, bromids, the purins, bile or blood. Very small concentrations of atabrine can be detected by using larger amounts of urine when available, say 500 cc., extracting with 200 to 250 cc. of ether, and finally with 8 to 10 cc. dilute hydrochloric acid.

The test of Wats and Ghosh²³ is similar in principle to the above. Alkalization is performed with potassium carbonate using 10 gm. to 100 cc. of urine, and extracting with amyl or isoamyl alcohol.

The extract has to be centrifuged to remove flocculent material and the clear supernatant fluid is examined in a small test tube in the usual way. The extract is very clear, and the test possibly slightly more sensitive than the first mentioned, but not as convenient. Contrary to the report of Wats and Ghosh, quinin, quini-din, plasmochin, acriflavin, or even urobilin may cause confusion. The test is probably better for quantitative purposes, colorimetrically, as described by Wats and Ghosh.

Summary. The administration of atabrine, an effective anti-malarial drug, is frequently followed by a yellow pigmentation of the skin which may last from 1 to 4 months or longer, after the drug has been discontinued.

The importance of the pigmentation lies not in any inherent body damage but in the diagnostic errors for which it may be responsible.

The diagnosis of atabrine pigmentation can be made by evaluation of the history of the patient, particularly with respect to previous antimalarial therapy, by study of the distribution of the pigmentation, and by application of one of the tests for detecting atabrine in the urine, as above described.

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LOCALIZED RADICULITIS AND NEURITIS: THEIR DIAGNOSIS AND TREATMENT.*

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THE diagnosis and management of *localized* radiculitis and neuritis is often difficult for the clinician and in many ways trying to the patient. *Multiple* radiculitis and multiple neuritis are, in the majority of cases, easy to diagnose: the widespread and usually symmetrical distribution of the sensory and motor manifestations indicate a systemic invasion by some infection, exogenous or endogenous poison, a deficiency state, or an extensive arthritis of the vertebral column. In localized radiculitis and neuritis the diagnosis is difficult for two reasons: it is often difficult to ascertain the structures involved, and it is usually even more difficult to make an etiological diagnosis.

Localized Radiculitis. Localized radiculitis may be caused by inflammatory or traumatic (pressure) lesions of the sensory or motor roots in the subarachnoid space, in the osseous intervertebral canals, and in their distal course to form plexuses or peripheral nerves. It must be borne in mind, however, that the sensory and motor symptoms are *segmental* (radicular) and *not peripheral in distribution*.

The sensory are the more common and conspicuous of the symptoms, with pain a constant feature. The pain may come on slowly or rapidly; it may be dull, sharp, shooting or lancinating; it may be constant or paroxysmal. Coughing and sneezing, as a rule, precipitate or intensify the pain, especially if the roots are intravertebrally implicated. The pain is often preceded, accompanied or followed by paresthesias or dysesthesias. There is usually some hyper-

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esthesia and hyperalgesia of the skin innervated by the involved roots, although the objective sensory disturbances may be minimal owing to the sensory overlapping. In severe and long standing cases there is an implication of deep sensibility manifested by loss of sense of position and ataxia. Tenderness over the nerve trunks is unusual, but Lasèque's sign is commonly observed and muscle activity frequently causes considerable discomfort.

When the motor roots are involved there is weakness, atrophy and changes in electrical reaction. Here, too, the distribution is segmental (radicular) and not peripheral, and for this reason the muscular weakness is partial. Trophic and vasomotor changes may occur, but are infrequent and herpes zoster may occur when the posterior spinal ganglion is implicated. Horner's syndrome (ptosis, miosis and enophthalmos) is observed when the eighth cervical and the first dorsal roots are involved.

Interesting spinal fluid changes have been observed in some cases of radiculitis. According to Feilung,¹ when the roots are implicated in the subarachnoid space, the spinal fluid shows a lymphocytosis. If the root is involved in the intervertebral canal (funiculitis) the spinal fluid shows an increase in albumin without lymphocytosis.

The *etiologic* diagnosis is the more difficult since radiculitis is rarely a primary or independent disease. Among the possible causes should be considered: extramedullary tumors of the spinal cord involving the root before it enters the intervertebral canal; meningitis of syphilitic, tuberculous or some other infectious origin; osseous diseases of the spine such as spondylitis (Gunther and Sampson²), tuberculosis, malignancy, trauma, or some extravertebral disease which affects the roots. Radiculitis may be the earliest or a prolonged expression of many of the above mentioned pathologic processes. In epidemic encephalitis radicular forms with neuralgic pains and clonic contractions of the muscles have been observed. Radiculitis also occurs in association with the primary infectious diffuse neuritis of Guillain and Barré³ and as a part of a myeloradiculopolyneuritis as reported by Strauss and Rabiner;⁴ and Sands.⁵

Generally speaking the etiologic diagnosis of radiculitis requires investigation for syphilis, tuberculosis or neoplastic disease, and each case should have a Roentgen ray of the region suspected as well as a lumbar puncture for pressure readings and spinal fluid studies. Failure to carry out such investigations will oftentimes lead to grief, both to the patient and the physician. It is likewise necessary to stress the necessity for repeated examinations and investigations.

In common with tabes, radiculitis of the lumbosacral region has ataxia of the lower limbs, Romberg's sign, diminution or loss of knee and Achilles reflexes and loss of deep sensibility. As a matter of fact, tabes is a radiculitis. The differential diagnosis of tabes de-

pend upon the finding of Argyll Robertson pupils and the serologic evidences of syphilis in the blood and spinal fluid.

Spinal cord tumors, especially of the extramedullary types, often begin with evidences of radiculitis. The eventual appearance of spinal cord symptoms and in particular a partial Brown-Sequard syndrome, with evidences of spinal subarachnoid block on lumbar puncture or campiodol injection, makes an early diagnosis possible in the majority of cases.

Myeloradiculitis or myeloradiculoneuritis (Strauss and Rabiner)⁴ occurs in young people and begins with an infection of the upper respiratory tract followed by the development of paralysis of the lower limbs with loss of tendon and skin reflexes, sphincter disturbances and subjective as well as objective disturbances in radicular distribution. The spinal fluid shows an increase in protein but little increase in cell count. The blood shows a slight leukocytosis. Recovery is rapid and complete. Sands⁵ regards these cases as belonging to the category of atypical epidemic encephalitis.

Osseous disease about the vertebral column is readily detected by Roentgen studies of the spine in anteroposterior and lateral views.

Pelvic tumors such as retroperitoneal sarcomas may cause radiculitis as has been frequently observed. *Repeated* rectal (and vaginal) examinations should be made in any case of radiculitis affecting the lower extremities. Superior sulcus tumors (Pancoast)⁶ may cause radiculitis of the upper extremities, and therefore, Roentgen ray studies of the lungs should be made in every such case as well as in every other case of radiculitis and neuritis when malignancy in any region is suspected.

Focal infection plays a doubtful rôle in the etiology of localized radiculitis. Only when all the other causes mentioned have been ruled out may one consider radiculitis to be due to some focal infection. Lastly, there are *idiopathic* cases in which no satisfactory cause can be found.

Treatment. Foremost in therapeutic importance is the finding of the underlying cause and its elimination. For the relief of pain in most cases, local applications of heat and diathermy should be tried or hot and cold packs may be applied. Such analgesics as acetylsalicylic acid, gr. v or x and amidopyrin, gr. v may be tried, but in severe cases codein and morphin are required. Foreign protein therapy (mixed typhoid vaccine, aolan) may afford relief in some cases and in others a lumbar puncture will sometimes alleviate a severe attack. In the most severe and persistent cases consideration of section of the posterior roots or chordotomy may be necessary. Ratera⁷ has reported favorable results from Roentgen ray treatment.

Localized Neuritis. Localized neuritis may be caused by direct trauma or pressure, by exposure to excessive cold (refrigeration), by extension of disease from adjacent structures, by exogenous and

endogenous poisons and by focal infections. Ofttimes no cause can be found.

Symptoms. The symptoms of simple neuritis vary with the cause and location of the disease but show somewhat common neurologic manifestations. There are sensory, motor, trophic, vegetative, reflex and electrical manifestations. The onset may be sudden or gradual, depending upon the cause, and usually without constitutional symptoms except that there may be slight fever. The prominent symptom is pain which follows the distribution of the affected nerve, and is of a burning, boring character, worse at night and increased by any movement of the affected part. The nerve is tender when pressed upon. Naturally pain is absent when the neuritis affects only motor nerves such as the facial or musculospiral. In these cases the only symptom is motor paralysis. Unpleasant sensations such as paresthesias (numbness, formication) and dysesthesia may precede, accompany, or follow the pain. Objective sensory disturbances are usually found in the more marked grades of neuritis of a sensory or mixed nerve, and involves all forms of sensation, *i. e.*, touch, pain, temperature, position and vibration. The intensity of the sensory impairment may vary from a slight reduction of sensation to a complete anesthesia. Some modalities of sensation, especially light touch and two-point discrimination, may be more affected than others. There may be increased sensitivity—hyperesthesia and hyperalgnesia—in some areas. It is to be stressed that all objective sensory disturbances in peripheral neuritis are within the cutaneous distribution of the affected nerves.

Since most of the peripheral nerves are mixed, motor disturbances are common in neuritis varying from a mild weakness to complete paralysis. If the condition is of sufficiently long duration the muscles become flabby and atrophic, with loss of deep reflexes, and the reactions of degeneration on electrical stimulation. Muscular fibrillation so common in anterior horn cell disease is an exception in peripheral neuritis and when encountered is usually of a coarse character.

Trophic and vasomotor disturbances are usually noted in peripheral neuritis, and are due to the involvement of sympathetic and trophic fibers which run in the peripheral nerves. The skin becomes bluish, thin, and glossy, or, more rarely, thickened, and the nails ridged and brittle. There may be alopecia, or, because of the atrophy of the skin, an appearance of hypertrichosis, and an increased or complete absence of perspiration. These trophic and vasomotor symptoms occur both in the mild and severe cases. In chronic neuritis, contractures of uninvolved muscles frequently occur due to overaction and the failure of opposition from the paralyzed antagonists. The diseased muscles often become actually

fibrosed and secondary joint changes of a fibrotic character with ankylosis is encountered.

Diagnosis of Neuritis. A diagnosis of neuritis is never simple or easy and is permissible only after the exclusion of the following conditions:

1. Local muscle, bone, joint and bloodvessel disease. Disability with pain about the shoulder may be due, not only to neuritis, but also to an arthritis of the shoulder joint, to a subacromial or subdeltoid bursitis, or to early malignancy (sarcoma). Sciatic neuritis is an unfortunate diagnosis when underlying causes, such as osteoarthritis of the spine and sacroiliac joints or a pelvic tumor are overlooked.

2. Radiculitis. Involvement of the spinal roots is characterized by sharp, shooting pains in the respective radicular area and is not accompanied by tenderness on pressure at the site to which the pain is referred.

3. Diseases of the spinal cord or brain. The paralysis and sensory disturbances of a neuritis should be differentiated from disease in the spinal cord or brain in which other signs of central nervous system involvement are definitely present, and tenderness over the nerve trunks is absent.

4. Neuralgia. This condition is characterized by darting and paroxysmal pain. Tenderness, when present at all is found only during paroxysms, with confinement to spots of definite localization. Even in chronic neuritis there is tenderness on pressure over the nerve trunks, weakness and flaccidity of the muscles.

Theoretically, the differential clinical diagnosis of localized neuritis and radiculitis is relatively simple; but practically, the etiologic diagnosis is most difficult except in those cases due to trauma or pressure. As a matter of clinical experience most cases diagnosed as localized "neuritis" turn out to be something else; many sciaticas have later proven to be spinal cord or pelvic tumors; an obturator neuritis, a hip joint disease; a brachial neuritis, a bursitis, periarthritis or sarcoma of the bones of the shoulder girdle. But even where such conspicuous causes are not obtainable the actual diagnosis is often difficult because of the bizarreness of the symptomatology and course of the disease as illustrated by the following cases:

CASE 1.—Severe pain in the left arm and shoulder without nerve tenderness. No disease of shoulder region or vertebræ found and no evidence of subarachnoid block. There developed weakness and absence of reflex of the left triceps muscle, atrophy of most of the muscles of the left arm, tenderness over the nerve trunks and irregular hypalgesia in the distribution of the 5th, 6th and 7th cervical segments. Slow but satisfactory recovery.

M. M., female, aged 35, laboratory technician, was admitted to the Graduate Hospital on August 31, 1934, complaining of pain in the left shoulder and left upper extremity. The family and past medical histories were irrelevant. She was in good health until August 23, 1934, when she

was awakened by pain in the left shoulder, arm, forearm and three ulnar fingers. There was no history of antecedent infection or exposure. The pain gradually diminished until August 31, when there was an acute exacerbation and after that she had intense pain with numbness in the above named distribution. The pain was constant with exacerbations, was not affected by movements of the shoulder and forearm, nor was it aggravated by coughing or straining at the stool. Elevation of the extremity gave her some relief. There were no symptoms referable to any other region in the body.

On admission the general physical examination was entirely negative.

Neurologic Status. The cranial nerves were negative except for a narrowing of the left palpebral fissure. *Upper Extremities.* There was no atrophy nor tremors. The left triceps muscle was definitely weaker than the right. The left triceps reflex was barely obtainable; the right was prompt and active; both biceps reflexes were exaggerated; there was no Hoffman's sign. There was diminution of pain sensation over an irregular area corresponding to the distribution of parts of the 5th, 6th and 7th cervical segments. There was no impairment of touch, cold and heat, nor of vibration. There was no tenderness over the nerve trunks. The *lower extremities* presented no abnormalities except a bilateral hyperreflexia with the left knee jerk slightly increased over the right. The abnormal reflexes were intact.

Course in the Hospital. Throughout her residence in the hospital from August 31, 1934, to October 2, 1934, the patient's temperature, pulse and respiration remained normal. In the course of a few days the weakness of the right biceps became much more pronounced and there appeared atrophy of the muscles between the scapulæ and the small muscles of the left hand. The movements of the various joints became painful and there was definite tenderness on pressure in the supraclavicular space, in the inner and upper aspect of the arm and in the forearm. The other findings were essentially the same as on initial examination. Except that the knee and Achilles jerks became markedly hyperactive, there were no sphincter disturbances. The pain was severe enough to require the continuous use of codein and morphin in addition to other forms of treatment.

Special Examination. Roentgen Ray Studies. The films of the teeth were entirely negative. A film of the cervical and dorsal spine (Dr. Karl Kornblum) revealed an abnormal curvature in the mid portion of the cervical spine which may have produced some encroachment upon the intervertebral foramina. *Urinalysis* was negative. *Blood Count:* Erythrocytes 4,830,000; hemoglobin 80% (14 gm.); leukocytes 6700; polymorphonuclears 61%; monocytes 1%; lymphocytes 38%. *Blood Chemistry:* Sugar 81 mg; urea nitrogen 16 mg. The blood Wassermann test was negative. A spinal puncture on September 21, 1934, showed an initial pressure of 180 mm. of water with a normal rise and fall on coughing, straining and respiratory movements and upon jugular compression. The examination of the fluid revealed no abnormalities as to cell count, protein, sugar, chlorids and the Wassermann test.

Condition on Discharge on October 2, 1934. She still had some spontaneous pain but was relatively comfortable. There was moderate weakness and definite wasting of muscles from the shoulder down to and including some of the muscles of the hand. Both the triceps and biceps reflexes on the left side showed definite impairment but could be elicited. No sensory impairment was noted at this time, but she did have considerable tenderness on pressure over the flexor surface of the forearm.

Treatment. On admission the patient was given sodium salicylate with sodium bicarbonate regularly and morphin when necessary. Heat and diathermy to the shoulder and cervical spines were administered daily. In addition, she received sodium amytal and other somnifacients which seemed

to be of little help to her. On September 14, 1934, she was given sodium salicylate, sodium iodine and colchicine intravenously, which was repeated every other day until the time of her discharge. This form and mode of medication produced a prompt and marked relief of pain.

Comment. When first seen the pain was not accompanied by definite objective findings and the diagnosis was difficult. In the course of a few days the clinical diagnosis of neuritis was relatively easy. The etiologic diagnosis in this case still remains a mystery. Neuritis of this sort has been noted following epidemics of gripe or occurring in patients who had none of the usual symptoms of gripe infection.

CASE 2.—Severe pain in the right shoulder, arm and forearm without nerve tenderness and not aggravated by movements of the joints. No disease of the shoulder region, of the vertebræ or of the lungs and found no subarachnoid block. Gradual developing weakness of the left biceps muscle, absence of the left biceps reflex and hypalgesia over distribution of 5th and 6th cervical segments. Transient loss of right abdominal reflexes; with pain improvement there appeared nerve tenderness and complete paralysis of the right biceps muscle. Complete recovery except for loss of power and absence of reflex in the right biceps.

A. W. H., aged 61, married, fuel merchant, was first seen on November 29, 1934, complaining of general weakness and fatigability. The family history was irrelevant.

About 30 years ago he went to Europe and took a "stomach cure." Since then he has been careful with his diet. He had two hernia operations, the last one 5 years ago. He had several nasal operations, the last one 3 or 4 years ago. He never drank or smoked. He did not take coffee and rarely tea. Two years ago he was accepted for life insurance. Thirty years ago he had an attack of pain in the left shoulder which lasted 6 weeks.

For 11 years he had had difficulty with a psychotic wife. Since 1929, he had serious business reverses and in the past year, after going into the oil business, had to be up every other night until midnight or later. For the past 3 to 4 years he had been treated for diplopia. About a year ago he noticed he was tiring very easily especially in the legs. He also had some pain in the back of his neck. The weakness in his legs had become progressively worse and about 4 weeks before admission, while reading at night, he reached backward and experienced a sensation as of the bed traveling with him. Following this incident he complained of vertiginous attacks off and on. Three weeks ago he was examined and found to have a blood pressure of over 200. A week later he developed what he called a cold without a nasal discharge or fever.

He had a feeling of fullness in the head which was constant, but no ringing in the ears, nausea or vomiting. He was constipated but the bowels were regulated by ordinary milk. There was no dyspnea except on exertion; no precordial pain, cough, nor expectoration; no nocturia; no numbness or pain in any of the limbs, but marked fatigability in the legs. His memory was not impaired and he slept moderately well.

Physical Examination. Weight 141½, pulse 80, blood pressure on the right side 165/90, on the left 170/90. The heart sounds were not unduly booming. The chest and abdomen were otherwise negative. The prostate was not enlarged. The peripheral vessels were satisfactory.

The neurologic examination was entirely negative.

On November 29, 1934, the following laboratory findings were reported: *Blood Count:* Hemoglobin 105% (Sahli); R. B. C. 5,400,000; color index

105 108; W. B. C. 9400; P. M. N. 63%; mono 2%; S. L. 28%; L. L. 7%; urea nitrogen 28 mg.; glucose 95 mg.; blood sedimentation 20 mm. in 1 hour. On reexamination the urea nitrogen was 13.5 mg.

Following the introduction of the needle for the withdrawal of the blood on November 29, 1934, he began to complain of pain in the right shoulder and arm. He blamed it on the venipuncture. It became progressively worse, was particularly annoying at night and was not relieved even by morphin. He was admitted to the Graduate Hospital on December 14, 1934, complaining of general weakness and soreness and more particularly of pain in the right shoulder and arm. This pain was constant but was much worse at night. It was of a boring nature and was not aggravated by movements of the shoulder or elbow joints and did not interfere with his walking. It was not made worse by coughing or straining at stool. It kept him awake at night and required continuous use of large doses of morphin.

The positive neurologic findings on December 13, 1934, included definite weakness of the right biceps muscle, absence of the right biceps reflex, hypalgesia and hypesthesia of the 5th and 6th cervical segments over the outer aspect of the forearm, diminution of the right abdominal reflexes and some increase of the knee and Achilles jerks on the right side as compared with the left.

Special Studies. Blood chemical tests were repeated and found to be normal. Urinalysis was essentially negative. Blood count revealed no definite abnormalities. Electrocardiogram was normal. The Roentgen ray of the lungs and shoulders were negative. That of the spine revealed a marked thoracic kyphosis with a compensatory cervical anterior curvature which might have encroached on the cervical nerves. On spinal puncture (December 22, 1934) the initial pressure was 160 mm. of water; there was a normal rise on straining and on light and heavy compression of the jugular veins. The examination of the fluid was negative in all respects.

Course in the Hospital. His pulse and temperature remained normal until his discharge from the hospital on December 30, 1934, except for a rise on the 19th of December following an injection of sodium salicylate, sodium iodid and colchicine. From December 14 until December 22, 1934, he required continuous administration of morphin and eodein and received as much as $1\frac{1}{2}$ grains of morphin in 24 hours to control the pain. His mentality differed, but he was generally depressed and irritable and when under the influence of drugs was at times slightly irrational. He was at no time incontinent. It was only in the latter part of December that his pain began gradually to subside while at the same time there appeared tenderness on pressure over the arm in the axilla and over the supraclavicular region.

At the time of his discharge on December 30, 1934, he had very little spontaneous pain, but considerable tenderness on pressure in the above-mentioned regions. The right biceps muscle was completely paralyzed; the right biceps reflex was abolished; there was a definite hypalgesia and hypesthesia in the distribution of the right 5th and 6th cervical segments.

Treatment. In addition to morphin and eodein an attempt was made to control his pain with acetylsalicylic acid and amidopyrin which was not successful. Improvement was first noted after the administration intravenously of sodium salicylate, sodium iodid and colchicine. On December 22, 1934 and for a time he received antipyrin, gr. v, methylene blue, gr. v, and extract of belladonna, gr. $\frac{1}{6}$, q.i.d. In addition he received radiant heat, diathermy, hot pads, alkalis and laxatives.

Subsequent Course. Two weeks after discharge he developed an acute pleurisy on the left side, from which he made a satisfactory recovery in about a week, but a week later developed a mild right-sided pleurisy. He returned to full duty 6 weeks after discharge from the hospital.

Comment. In this case as in the first, with pain as the initial feature, the clinical diagnosis of neuritis could not be made at the outset and was not possible until after other conditions had been excluded by spinal puncture, Roentgen ray of the chest and shoulder and other studies. The etiologic diagnosis is still unknown. The subsequent attacks of pleurisy would tend to show that he had a systemic infection the source of which had not been determined.

CASE 3.—Pain in the lower back for 2 years, particularly noticeable after working or long driving in his automobile. Sudden cramplike pains radiating from the buttock to the ankle, and numbness of ankle and foot. Diagnosis of lumbosacral radiculitis and left sciatic neuritis. After a deeply situated abscess in the right tonsil was evacuated and later the tonsils removed, the patient improved rapidly.

This patient came under observation on January 16, 1935, with the complaint of excruciating pain in the back and left lower extremity. He had had pain in his lower back off and on for a period of 2 years with intervals of days or even 2 or 3 weeks when there was no pain or soreness whatsoever. Suddenly, in the latter part of December, 1934, he developed sharp and acute pain in the left lower extremity radiating from the lumbar region to the ankle. There was no history of acute or chronic infection or other condition which might have had any bearing except possibly his back injury 3 years before.

The neurologic examination showed no disturbance of the cranial nerves or upper extremities. The abdominal reflexes were present and equal. There was marked fixation of the muscles of the back and a loss of the lumbar lordotic curve with a compensatory scoliosis. The right knee and ankle jerks were slightly hyperactive, but the left knee and ankle jerks were diminished. There was marked tenderness over the lumbar and sacral vertebrae and also over the sciatic nerve. Lasague's sign was positive on the left side and negative on the right. There was impairment of touch, pain and temperature sense in the distribution of the 1st, 2d, 3d and 4th sacral nerve roots. Vibratory sensibility was lost in the toes of the left foot and impaired in the ankle and tibia on the left side. There was marked impairment of position sense in the toes and ankle on the left. Any movements of the lower back produced excruciating pain. It was with difficulty that the patient could arise from a chair or couch and he needed assistance when walking. He improved steadily under treatment for a period of about 3 weeks, then suddenly developed a chill and fever followed by profuse perspiration. From that time onward he had irregular attacks of chills and fever (never over 101°) for a period of 2 weeks. He lost weight, his appetite became poor, and he looked very distinctly ill. Two suspicious teeth were removed, but inasmuch as the chills and fever did not clear up he was referred to an otolaryngologist who found a peritonsillar abscess containing 1 or 2 drams of pus on the right side. After draining this abscess the chills and fever promptly subsided and the pain in his back and leg improved steadily. Following tonsillectomy 3 or 4 weeks later further improvement occurred, and when last seen he was nearly well.

The neurologic examination at this time was as follows: The fixation of the back muscle had entirely disappeared and bending movements were much less restricted. Slight fibrillations were noted in the gluteal muscles on the left side when contracted. The knee jerks were present, active and equal bilaterally. The right ankle jerk was slightly hyperactive and the left diminished. Vibratory sense was normal on both sides. There was diminution of pain and touch sense in the distribution of the nerve roots previously mentioned, but it was quite evident that it was rapidly clearing up. Lasague's sign was still mildly positive on the left side, but absent

on the right. There was noted a slight wasting of the muscles of the left thigh and leg. The patient stated that he had mild discomfort in the left lower extremity on motion, but no sharp or acute pain. If he did too much walking or bending he had a slight aching in the lumbosacral region of the back.

The laboratory investigation showed a perfectly normal blood count, negative urinalysis and normal blood chemical findings. The Roentgen ray studies showed abscess at the apices of 2 teeth and left lumbosacralization with rudimentary left lumbosacral joint. Otherwise all studies were totally negative.

Treatment. Before coming to our attention the patient had had all kinds of hypnotics and sedatives with no particular relief of his symptoms. As soon as the diagnosis of radiculitis and neuritis had been made he was placed upon intravenous injections of sodium salicylate, sodium iodid and colchicine. He also received 5 or 6 Roentgen ray treatments over the lower spine. Heat was applied daily to the lumbosacral region and the patient was kept more or less quiet in bed. He improved very rapidly so that in about 3 or 4 weeks' time no medication was given except pyramidon by mouth.

Comment. This patient with a history of intermittent radiculitis over a period of 2 years very suddenly displayed an acute radiculitis and sciatic neuritis with definite objective neurologic disturbances. With removal of focal infection and treatment as outlined a rapid improvement was experienced. The diagnosis was relatively easy from the disease classification standpoint, but the etiologic factor was not discovered until retraction of the right tonsil disclosed a peritonsillar abscess.

Comment. In the treatment of non-traumatic cases of neuritis the *removal of the cause* is of first importance. Particular attention should be directed to the elimination of focal infections and after this, prolonged rest of the affected part with the application of splints to the limbs to procure immobilization. For the direct relief of pain local applications of heat, especially moist heat—as from steam, poultices, or hot fomentations—are useful. Occasionally in the early stages the use of ice, locally applied, gives some relief. Counter-irritation by mustard plasters or other agents is efficacious. Sometimes the galvanic current, used in strength sufficient to redden the skin, gives immediate relief.

Internally the best agents are the salicylates and especially acetylsalicylic acid with amidopyrin. The iodids appear to be useful. Stark⁸ has obtained satisfactory results from the employment of large doses of sodium iodid intravenously, administering from 30 to 120 grains intravenously without untoward effects. A combination of salicylates, colchicine and iodids when given intravenously has proven in our experience to be most valuable. In many cases the pain may be so severe that it is necessary to resort to morphin and its derivatives.

In severe and protracted cases the following measures have been suggested: hot air applications, the use of electric currents, cataphoresis, counter irritation with hydrochloric acid and injection of alcohol.⁹

Attention should be directed to the general health of the patient with respect to nutrition and elimination, employing laxatives, diuretics, tonics and alteratives as indicated. After the subsidence of the acute symptoms and all tenderness and pain have disappeared baking, massage and faradic stimulation help in restoring the function of the disabled muscles and overlying tissues.

Summary. Except in cases resulting from known trauma, the *diagnosis* of localized radiculitis and neuritis should be made with caution. In the majority of cases these conditions are secondary to disease of the spinal cord and its meninges, the vertebral column and other osseous structures, the pelvis and lungs, focal and general infections and intoxications. The primary or idiopathic forms are rare and are so diagnosed only by the failure to find a definite cause. In the majority of cases it requires the study of spinal fluid (pressure, cytology, chemistry, Wassermann test, etc.), a Roentgen ray study of the region concerned and usually of the spine, a rectal (and vaginal) examination as well as *repeated* general physical and neurologic examinations and routine blood studies.

The *prognosis* depends upon the underlying causes and severity of the case. When the cause can be removed, providing the roots and nerves are not actually destroyed, the outlook is good. In primary cases the outlook is favorable as to recovery and usefulness in the majority of cases, but it is to be borne in mind that the duration of some of the cases is extremely long and accompanied by a great deal of suffering.

In the treatment of the secondary forms the removal or correction of primary causes is of first importance. In the symptomatic treatment the use of the various salicylates, amidopyrin and a combination of iodids, salicylates and colchicine intravenously are helpful. Immobilization; moist, dry and radiant heat, as well as diathermy may bring relief. In the majority of cases opiates are required during the acute stage.

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IS THERE ANY RELATIONSHIP BETWEEN RESISTANCE AND SUSCEPTIBILITY TO POLIOMYELITIS AND DIPHTHERIA?*

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THE obscure nature and debatable mechanism of natural insusceptibility to poliomyelitis in man has prompted us for a number of years to give close attention to the various aspects of this problem as far as they are applicable to a study of the experimental disease.^{1,2,3} One important part of this program has dealt with determining the limits of specificity in the inactivation of poliomyelitis virus by serum. Experiments undertaken for this purpose have revealed, on the one hand, a narrow specificity of the neutralization phenomenon in that a large number of various antibacterial and antiviral immune sera proved incapable of bringing about inactivation of the virus. On the other hand, it was found that certain samples of antitoxic sera from horses immunized against diphtheria toxin, scarlatinal streptococcus toxin and rattlesnake venom, when tested under the same conditions, possessed the property of effecting neutralization of the virus *in vitro*. In conformity with these findings, poliocidal substances were occasionally demonstrable in the serum of monkeys actively immunized against diphtheria toxin.⁴

Another approach to the same problem centers around attempts to induce enhanced resistance to poliomyelitic infection by other than specific means. Experiments undertaken by Armstrong and Harrison⁵ have shown that monkeys may acquire a relative increase in resistance to poliomyelitic infection following immunization with diphtheria toxoid. Our own experience on that point is fully in harmony with the observations of these authors. In a fairly comprehensive series of animals, immunization with either diphtheria toxoid or toxin-antitoxin mixture increased the resistance of nearly one-half of the monkeys in various degrees to subsequent intracerebral inoculation with multiple paralytic doses of poliomyelitis virus.⁴

While no clear explanation can be given, at present, to account for the overlapping protection in the animal or the common reactivity of the serum, it is of interest to note that diphtheria toxin seems to be susceptible to inactivation by certain highly specialized biological substances which are also capable of neutralizing poliomyelitis virus. Thus, contact *in vitro* with adrenalin,^{6,7} cortin^{7,8} and vitamin C (ascorbic acid⁹) is apparently equally destructive for both the toxin of the diphtheria bacillus and the virus of poliomyelitis.

In order to extend the experimental basis of our observations it has seemed advisable to carry out additional neutralization tests with

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diphtheria antitoxic horse sera obtained from different sources. At the same time, we have enlarged our series of monkeys actively immunized against diphtheria toxin before infection with poliomyelitis virus. It is the object of this paper briefly to report the results obtained in this work and to discuss in more detail the conclusions which suggest themselves.

Experimental Work. I. VIRUCIDAL TESTS WITH DIFFERENT DIPHTHERIA ANTITOXIC HORSE SERA. A total of 16 samples of antitoxic sera obtained from horses under immunization against diphtheria toxin were employed in these tests. The sera were secured through the courtesy of various State and commercial laboratories and we wish to express here our appreciation for the cordial coöperation received from these institutions. All sera were fresh, unpreserved trial bleedings taken during the course of immunization, with both high and low titers of antitoxin. The technique of the neutralization test followed the usual technique adopted in this laboratory, *i. e.*, incubated mixtures of 0.9 cc. of serum and 0.1 cc. of a 10% virus suspension were injected intracerebrally into individual monkeys. The experiments were controlled by the inclusion of an adequate number of animals inoculated with the same dose of virus plus saline or normal monkey serum (Table 1).

TABLE 1.—NEUTRALIZATION OF POLIOMYELITIS VIRUS BY ANTITOXIC DIPHTHERIA HORSE SERUM.

Diphtheria serum.	Anti-toxin unitage.	Neutralization test.			
		Monkey No.	Result.	Control monkey.	Result.
Lederle 6750	?	Q2	Complete paralysis 12 d.	Q13 Q26	Complete paralysis 8 d. Partial paralysis 9 d.
Mulford 674	?	Q5	No paralysis		
" 676	?	Q6	Complete paralysis 8 d.		
" 677	?	Q7	Partial paralysis 8 d.		
" 678	?	Q8	No paralysis		
N. Y. State Dept. Health 469	600	Q10	Complete paralysis 8 d.	Q90	Complete paralysis 7 d.
" " 471	500	Q11	" " 9 d.		
" " 466 ¹	400	Q12	" " 7 d.		
" " 466 ²	800	Q24	Partial paralysis 10 d.		
N. Y. City Dept. Health 635 ¹	110	O76	Partial paralysis 19 d.		
" " 635 ²	110	O91	Complete paralysis 8 d.	M78 M79	Complete paralysis 11 d. Complete paralysis 8 d.
" " 818	225	O94	" " 11 d.		
" " 819	85	O95	" " 6 d.		
" " 820	110	O96	No paralysis		
" " 826	375	O97	Complete paralysis 8 d.		
Mass. State Dept. Health 636 Normal	?	M84	No paralysis	M70	Almost complete paralysis 11 d.
" " 636 Diph.	235	M85	No paralysis		
Mass. State Dept. Health 636 Normal	?	M64	No paralysis		

It will be seen from Table 1 that unquestionable neutralization of the virus occurred with four different samples while a fifth serum was capable of prolonging the incubation period to the 19th day after injection. If the figures are considered *in toto*, it follows that approximately one-third of the various samples of diphtheria antitoxic horse sera were capable of bringing about either complete or partial inactivation of the virus *in vitro*. These results are therefore essentially in keeping with our previous observations.⁴ Again, we failed to observe any consistent relationship between antitoxic potency, as expressed in unitage, and extent of poliocidal power.

Of particular interest are the results obtained with the normal serum (No. 636), which inactivated the virus on repeated tests. On further examination it was discovered that this particular sample of normal horse serum contained an unusually high content of natural antitoxin, since 1 cc. of serum injected subcutaneously protected guinea-pigs against a simultaneous similar injection of 5 and even 20 m.l.d. of diphtheria toxin.

II. EXPERIMENTAL POLIOMYELITIS IN MONKEYS ACTIVELY IMMUNIZED AGAINST DIPHTHERIA TOXIN. Four rhesus monkeys were given a series of subcutaneous injections of either toxin-antitoxin mixture or of toxoid. After a ground immunity was thus established, these animals received further injections of straight diphtheria toxin, increasing gradually from 5 m.l.d. to 100 m.l.d. The large amounts of potent toxin were well tolerated by 3 monkeys which showed no more than a slight flush or occasionally a superficial ulceration at the site of injection. The fourth animal however, which had reacted more severely to every injection, succumbed to the last dose of toxin, *i. e.*, 100 m.l.d., with characteristic symptoms of diphtheria intoxication. The 3 animals which received the full course of immunization were injected intracerebrally with 0.1 cc. of a 10% suspension of poliomyelitis virus. None developed paralysis although one showed some fever and slight awkwardness in jumping for a few days. Two months later, these 3 animals were reinfected intracerebrally with 0.5 cc. of a 10% virus suspension. Nine and 14 days respectively after reinfection, 2 showed a slight paresis of the arm which did not progress any further. The third animal remained entirely free from any symptoms of the disease. Adequate controls accompanied both of these tests.

Samples of serum were obtained from the 4 animals described above at the early, intermediate and late stages of the immunization period and were tested for virucidal properties. Of those taken early, 1 serum inactivated the virus completely and 3 partially (incubation period over 14 days). When the animals were bled again, 1 month later, none of the 4 sera gave any indications of the presence of virucidal substances. Serum was finally obtained from the 3 monkeys which survived the injection of the last dose of toxin. Of these 3 samples, 1 only inactivated the virus (Tables 2 and 3).*

These experiments confirm our previous observation that active immunization against diphtheria toxin is frequently followed by a relative increase in resistance to poliomyelitic infection. However, while polioeidal substances are sometimes demonstrable in the serum of such immunized animals, their appearance is evidently very irregular, shows no correlation to the degree of the antitoxic immunity and their concentration at best is only very weak.

Discussion. The important part played by non-specific agencies in the prophylaxis and cure of infectious diseases, particularly with respect to the enhancement of cellular defense activity, has long been recognized by immunologists. Cross protection between two totally different diseases, however, rarely simulates an immuno-

* Three of the serums which had partially inactivated the virus in our hand were sent to Dr. N. P. Hudson of the University of Chicago who kindly agreed to carry out comparative tests. All 3 serums failed to show any evidence of virucidal power. It would seem from this experience that borderline results in neutralization tests which are obtained with one strain of virus and one particular technique cannot be duplicated at will with another strain and another technique. This fact, in our opinion, does not militate against acceptance of "partial neutralization" as a definite phenomenon in a well controlled series carried out with highly virulent virus. It may, however, explain some of the discrepancies that have been reported from different laboratories,¹⁰ except when very potent sera are examined with which full agreement is usually obtained.¹¹

logical interrelationship of the sort suggested by our experiments for diphtheria and poliomyelitis. It seems to us that a satisfactory explanation of this phenomenon cannot be given along traditional lines of immunological thinking. Instead of seeking for some antigenic relationship we believe that the search should rather be directed toward the discovery of a common pathologic or physiologic reaction of the host to the two agents of disease.

TABLE 2.—POLIOMYELITIS INFECTION IN MONKEYS AFTER ACTIVE IMMUNIZATION AGAINST DIPHTHERIA.

Donor monkey No.	Type of immunization.	Date infected.	Result.	Control monkey.	Result.
L62	Toxin-antitoxin first; later toxin	5/26/34 7/17/34	No paralysis Slight paresis arms 9 d.	M42 M76	Complete paralysis 8 d. Complete paralysis 7 d.
L64	Toxin-antitoxin first; later toxin	Died before infection			
L65	Toxoid first; later toxin	5/26/34 7/17/34	No paralysis Slight paresis arms 14 d.	M42 M76	Complete paralysis 8 d. Complete paralysis 7 d.
L66	Toxoid first; later toxin	5/26/34 7/17/34	No paralysis No paralysis	M42 M76	Complete paralysis 8 d. Complete paralysis 7 d.

TABLE 3.—VIRUCIDAL TESTS WITH SERA OF MONKEYS AFTER ACTIVE IMMUNIZATION AGAINST DIPHTHERIA.

Donor monkey No.	Date bled.	Virucidal test.			
		Test monkey.	Result.	Control monkey.	Result.
L62	4/10/34	L82	No paralysis	M11	Complete paralysis 9 d.
	5/11/34	M69	Complete paralysis 10 d.	M12	Complete paralysis 6 d.
	5/16/34	M55	No paralysis	M70	Complete paralysis 11 d.
L64	4/10/34	L85	Partial paralysis 15 d.	M54	Complete paralysis 6 d.
	5/11/34	M58	Complete paralysis 10 d.	M11	Complete paralysis 9 d.
				M12	Complete paralysis 6 d.
L65	4/10/34	M22	Slight paresis 15 d.	M32	Complete paralysis 8 d.
	5/11/34	M59	Partial paralysis 10 d.	M70	Complete paralysis 11 d.
	5/16/34	M56	Complete paralysis 11 d.	M54	Complete paralysis 6 d.
L66	4/10/34	M23	Complete paralysis 16 d.	M32	Complete paralysis 8 d.
	5/11/34	M100	Complete paralysis 10 d.	M95	Complete paralysis 7 d.
	5/16/34	M59	Partial paralysis 9 d.	M54	Complete paralysis 6 d.

It is profitable to begin this discussion by emphasizing certain important analogies in the pathology of the two diseases which may be overlooked because of fundamental differences in the primary seat of the lesions. The well known neurotropism of diphtheria toxin, which leads to postdiphtheritic peripheral paralysis, is characteristically reflected in the frequent occurrence of acute degenerative changes in the central nervous system of experimental animals after the injection of diphtheria toxin,¹² particularly in the spinal cord of monkeys.^{4,13} An intimate relationship to changed endocrine func-

tion (thymus, pituitary, gonads, adrenal) and lymphatic hyperplasia is suggested by numerous clinical and pathologic observations for both, diphtheria^{9,12,14,15,16} and poliomyelitis.^{9,17,18,19}

Obviously, any similarity in the physiologic reaction of the host should reveal itself most clearly in the comparative degree of susceptibility to the two diseases. As early as 1913, the well known clinician Baginsky²⁰ in his monograph on diphtheria writes upon this subject as follows: "I have been struck with the very extraordinary sensitivity of children suffering with such diseases of the central nervous system as poliomyelitis, spastic cerebrospinal paralysis, hemiplegia, etc. One is scarcely able to keep these children in the hospital wards free from infection with diphtheria." Peabody, Draper and Doehez,²¹ in their monographic study of poliomyelitis, mention the case of a "child dying of a laryngeal diphtheria two months after the onset of poliomyelitic paralysis affecting both legs." A similar thought is expressed in a recent paper by Seckel¹⁴ who discusses the predisposition of certain constitutional types to the severe and lethal forms of diphtheria. Thus, a group of 6 cases of extraordinary severe toxic diphtheria, with 5 deaths, included 2 children which had previously been attacked by poliomyelitis.

With the advent of the Schick test as a more convenient method for measuring susceptibility to diphtheria, further interesting contributions to this subject were made. During the 1916 epidemic of poliomyelitis in New York City, Zingher²² noted an abnormally high percentage of positive Schick reactions among children suffering from poliomyelitis (75.6%) as compared with either normal children of similar age groups (21.4%) or with children sick with measles (34.2%) or scarlet fever (45.3%). To quote from this author: "Between 1 and 4 years of age there is an average of over 80% of positive reactions. This percentage is based on over 1000 cases and can therefore be accepted as being fairly accurate. It was interesting and striking to see in the wards of the Willard Parker Hospital row after row of children who gave a positive Schick reaction. Indeed at one time the number of positive tests in this age group reached between 90 and 95%." This experience agrees well with our observation that the power of normal human serum to neutralize poliomyelitis virus frequently coincides with a negative Schick reaction of the individual.⁴

Comparable data for the 1931 outbreak in New York City are not available. However, Landon and Smith¹⁷ state that at the same hospital, in 1933, among 273 cases of poliomyelitis, 40% showed positive Schick reactions and 51% negative reactions, the remainder not having been recorded. This reduction in the number of positive reactors, according to these authors, "is accounted for by the fact that during this fifteen-year period the widespread immunization of children by diphtheria toxin-antitoxin or toxoid has been carried out." Closely similar observations were made during the Philadelphia

epidemic in 1932 by Henry and Johnson²³ who report that of 304 poliomyelitis patients admitted to the Philadelphia Hospital for Contagious Diseases 51.3% gave a history of having had diphtheria toxin-antitoxin previously. If we assume that a majority of these immunized children had also negative Schick reactions, one might feel inclined to take the recent observations in New York and Philadelphia as indicating that Schick-negativeness produced by artificial means has little or no effect on susceptibility to poliomyelitis in man. Without further statistical analysis, however, such a conclusion may prove erroneous. First, it should be remembered that there has been a marked trend in recent epidemics (New York City cases under 5 years: 1907, 86.8%; 1916, 79.2%; 1931, 53.3%; 1935, 32.8%—Philadelphia cases under 5 years: 1916, 71.1%; 1932, 51.5%) for an advance in the age line. This would tend automatically to reduce the actual number of positive tests which may be expected in a group of poliomyelitis patients. Second, neither report includes figures that permit a strict comparison with the present normal child population, the exact percentage of negative Schick reactors among which may conceivably be considerably higher—because of widespread active immunization—than the observed figure of roughly 50% for the poliomyelitis patients. Finally, it remains to be determined whether or not preceding antidiphtheritic immunization, even if it fails to reduce the incidence of poliomyelitis, serves to lower the mortality or the frequency of severe residual paralysis in this disease. These questions must be answered before any definite conclusions are warranted. The point is of more than passing interest in view of the unexplained shift in the age distribution and the lower fatality observed in recent epidemics of poliomyelitis in the United States.

We have made an attempt to gather further data on this interesting problem, particularly as regards the relative frequency of diphtheria and poliomyelitis in the same child. With the kind assistance of Dr. William H. Best, Director of the Bureau of Preventable Diseases, New York City Department of Health, a questionnaire was prepared which was mailed to physicians in Greater New York who had reported cases of infantile paralysis to the Department during the years of 1931–1932. This questionnaire asked for detailed information on the type of case reported, the absence or presence of previous attacks of diphtheria, and any other data which were available on preceding antidiphtheritic immunization. Of a total of 350 questionnaires sent out, only 182 were returned with partial or complete answers. Among these were 16 cases giving a definite history of having had diphtheria before the attack of poliomyelitis. This would tend to indicate a greatly increased incidence of diphtheria among our group of poliomyelitis patients (ages mostly 1 to 10 years) when contrasted with the attack rate of diphtheria for the child population at large in New York City in

the standard age group of 1 to 9 years during the same period which varied from 1.97 per 1000 to 1.2 per 1000. While the two sets of figures are admittedly of too uneven size for any fair comparison, these results reinforce the impression gained from a study of the literature that the type of child which is predisposed to poliomyelitis is also highly susceptible to diphtheria. Precise data as to the absence or presence of previous antidiphtheritic immunization and the clinical type of the disease were obtained from 165 returns. Among a group of 70 cases of poliomyelitis developing in children previously immunized against diphtheria (46 definitely stated as negative) 45 (64.22%) were of the paralytic type and 25 (35.7%) were listed as abortive. The other group of 95 cases of poliomyelitis developing in children which gave no history of previous antidiphtheritic immunization included 75 paralytic cases (78.95%), and 20 abortives (21.05%). Again, the statistical material is too small for any valid conclusions to be drawn although it would seem that the incidence of paralysis was somewhat reduced in the diphtheria-immune children.

We believe that the data presented in this paper and reviewed above are strongly suggestive of the operation of some common basic mechanism which governs susceptibility and resistance to both, poliomyelitis and diphtheria. To establish definite proof of such a relationship will require more extensive research. It is hoped that this communication will stimulate further experimental and epidemiologic observations which will help to clarify this problem.

Summary and Conclusions. 1. In a series of neutralization tests with 16 diphtheria antitoxic horse sera, complete inactivation of poliomyelitis virus occurred with four samples and partial inactivation with one sample. There was no relationship between antitoxic potency and poliocidal power.

2. Three monkeys which survived a full course of active immunization against diphtheria were protected against intracerebral infection with poliomyelitis virus. Upon reinfection, two animals developed a slight paresis, the third remaining entirely free from any symptoms of the disease.

3. Poliocidal substances, although occasionally demonstrable in the serum of diphtheria-immune monkeys, appear with marked irregularity, show no correlation to the degree of antitoxic immunity and their concentration at best is only very weak.

4. The problem of non-specific resistance and susceptibility to diphtheria and poliomyelitis is discussed in the light of clinical and pathologic observations.

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RELATION OF PHYSICAL DEFECTS TO NUTRITIONAL IMPAIRMENT, BASED ON THE EXAMINATION OF 30,000 CHILDREN OF 21 STATES.

PHYSICAL MEASUREMENT STUDIES NO. 5.*

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Of the four earlier papers¹⁻⁴ of the series, two have been devoted to the matter of physical defects in children, and more specifically, to the study of the relation of physical defects to physical growth. It is purposed in this, the fifth paper, to examine the relation of physical defects to nutritional impairment, and for several reasons: There has been a steadily increasing interest in nutrition and its various ramifications; methods of measuring nutrition continue in a chaotic state, and while it is generally agreed that a positive association exists between certain physical defects and nutritional impairment, there is no unanimity of thought upon the question of the order of magnitude of such association.

It is unnecessary at this time to review the methods of judging nutrition and what are believed to be the causes and effects of malnutrition. This has been done recently by Roberts⁵ in several chapters which include classified lists of pertinent references for further study.

Material and Method. An opportunity to investigate the subject proposed is afforded by data collected by three officers of the United States Public Health Service in connection with the physical measurement of approximately 30,000 white children from 6 to 15 years† in 21 States. The officers who made the measurements are Drs. V. R. Anderson, E. B. Sterling and M. V. Veldee. The 21 States are: Maine, New Hampshire, Vermont, Massachusetts, Connecticut, New York, New Jersey, Pennsylvania, Minnesota, Wisconsin, Michigan, Indiana, Illinois, Texas, Louisiana, Arkansas, Tennessee, Kentucky, Missouri, Utah and Nevada. For the geographic distribution of the children according to State and community and other pertinent information the reader is referred to the previous papers of the series.

The group of children under consideration is a homogeneous one in several respects: The children are native-born of white native-born parents and grandparents; all lived in large urban areas, and none seriously ill is included since all were attending school. Furthermore, grossly defective or crippled children are excluded.

Before the child was measured and after its outer clothing had

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† The small number of 15-year-old children measured are excluded.

been removed the nutrition was judged by the Public Health Service officers and recorded as excellent, good, fair, poor or very poor without reference to existing standards of height and weight. The nutrition of the child was judged by its general appearance, activity, the condition of its skin, amount of subcutaneous fat, muscle tone, alertness and vitality.

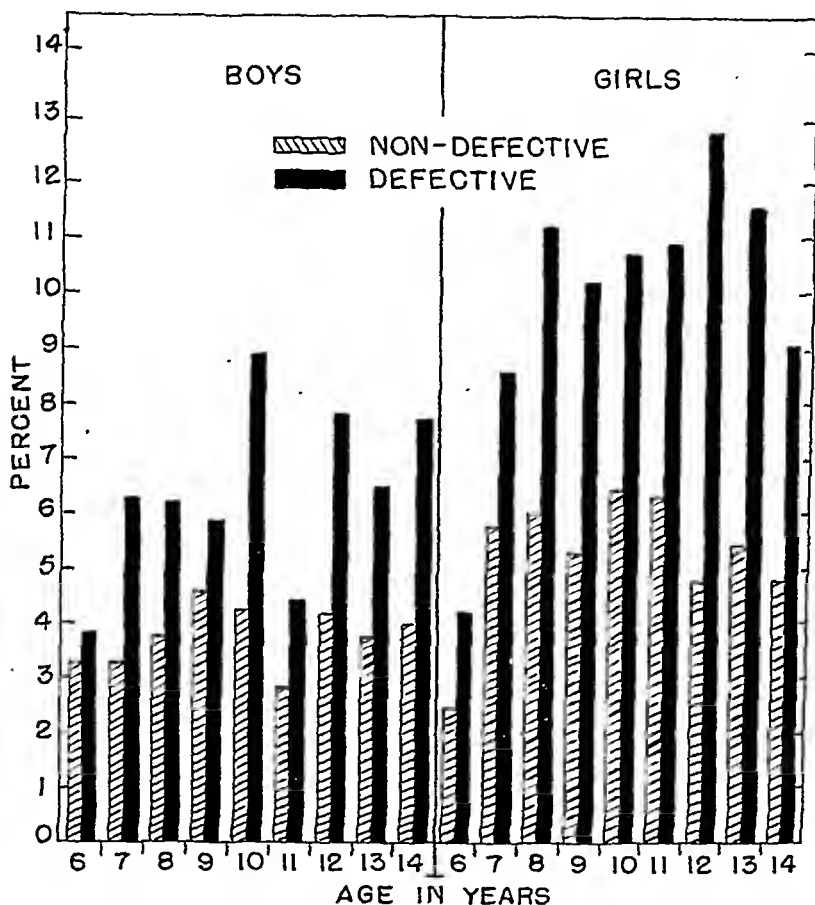


FIG. 1.—Per cent of boys and girls with and without physical defects judged poor or very poor with respect to nutrition.

The presence of physical defects was also noted. These defects had been observed in the majority of the children by the local school medical officers shortly before the physical measurements were made, and were accepted and recorded by the officers of the Public Health Service as defects existing at the time of measuring. Those children who had not been previously examined for defects were examined for them by the officers making the measurements. The defects which include, principally, carious teeth, defective tonsils

and adenoids, alone or in combination, were recorded for almost one-half of the children measured. The reader who is interested in the composition of the defective group is referred to a table in an earlier publication³ where the number of boys and girls with recorded physical defects is classified according to specific defects. The small discrepancy between the total number of children given in the table and the number given later in this paper is because of the few children that had no nutritional status recorded for them.

It is now logical to ask whether the physical defects as noted are associated with the physicians' judgment of poor or very poor nutrition, and should an association be demonstrable it may be concluded, presumably, that the physical defects are associated with nutritional impairment. Or stating the question in other words: Are the non-defective and defective children different with respect to nutritional impairment? At the same time some light will be thrown on the question of the order of magnitude of the association, if present. Because of the small numbers resulting when the different nutritional classes are divided into groups specific for sex and age, and to minimize the effect of the possible existence of a difference of opinion among examiners as to which particular nutritional class should be recorded in a particular case, it was decided to combine the nutritional classes into 2 broad groups: (a) Excellent, good and fair, and, (b) poor and very poor. The attempt to answer the question proposed includes the determination of the percentages of children judged poor or very poor in the non-defective and defective groups, specific for sex and age, followed by an investigation of the statistical significance of the differences between the calculated percentages.

Results. Of the total number of 14,070 boys examined and judged 6293 (44.7%) had one or more physical defects recorded for them. Similarly, of the 14,157 girls, 6369 (45%) had one or more physical defects recorded for them. Table 1 shows the number of non-defective and defective children together with the number and per cent of these groups that were judged poor or very poor with respect to nutrition, classified according to sex and age. It will be observed that 6.5% of the boys of all ages with physical defects had a nutritional status of poor or very poor while the per cent for the physically non-defective is 3.8. The corresponding per cents for the girls are 10.2 and 5.4, respectively. While the difference between the per cents for the girls is almost twice the corresponding difference for the boys, both differences, namely, 4.8 and 2.7, respectively, are statistically significant. In this experience, therefore, when all ages are combined, boys or girls with physical defects are probably different from boys or girls without physical defects with respect to nutritional impairment as judged by the physicians; in other words, physical defects are associated with nutritional impairment, and with the order of magnitude as indicated.

With respect to specific ages, Table 1 and Fig. 1 show that the

proportion of physically defective girls judged poor or very poor in nutrition is consistently greater than the corresponding proportion for the boys. For the girls the per cents range from 4.2 to 12.9; for the boys, from 3.8 to 8.9. For both sexes the lowest per cent is yielded by the children of the youngest age. Other than this the two ranges of per cent shows no similarity with respect to changes in age.

TABLE 1.—NUMBER AND PER CENT OF BOYS AND GIRLS WITH AND WITHOUT RECORDED PHYSICAL DEFECTS JUDGED POOR OR VERY POOR WITH RESPECT TO NUTRITION.

		[Defective group in <i>italics</i> .]					
		Boys.				GIRLS.	
Age in years.		Total.	Poor or very poor nutrition.		Total.	Poor or very poor nutrition.	
			No.	%.		No.	%.
All ages		7777	296	3.8	7788	421	5.4
		<i>6293</i>	<i>407</i>	<i>6.5</i>	<i>6369</i>	<i>649</i>	<i>10.2</i>
6		521	17	3.3	497	12	2.4
		<i>396</i>	<i>15</i>	<i>3.8</i>	<i>457</i>	<i>19</i>	<i>4.2</i>
7		725	24	3.3	744	43	5.8
		<i>867</i>	<i>55</i>	<i>6.3</i>	<i>803</i>	<i>69</i>	<i>8.6</i>
8		783	30	3.8	794	48	6.0
		<i>890</i>	<i>55</i>	<i>6.2</i>	<i>854</i>	<i>96</i>	<i>11.2</i>
9		845	39	4.6	848	45	5.3
		<i>961</i>	<i>57</i>	<i>5.9</i>	<i>919</i>	<i>94</i>	<i>10.2</i>
10		832	36	4.3	954	61	6.4
		<i>857</i>	<i>76</i>	<i>8.9</i>	<i>810</i>	<i>87</i>	<i>10.7</i>
11		985	28	2.8	995	63	6.3
		<i>743</i>	<i>33</i>	<i>4.4</i>	<i>724</i>	<i>79</i>	<i>10.9</i>
12		1078	45	4.2	1073	52	4.8
		<i>631</i>	<i>49</i>	<i>7.8</i>	<i>660</i>	<i>85</i>	<i>12.9</i>
13		1122	42	3.7	1033	56	5.4
		<i>522</i>	<i>34</i>	<i>6.5</i>	<i>628</i>	<i>73</i>	<i>11.6</i>
14		886	35	4.0	850	41	4.8
		<i>426</i>	<i>33</i>	<i>7.7</i>	<i>514</i>	<i>47</i>	<i>9.1</i>

With regard to the sex-age specific proportions with poor or very poor nutrition in the non-defective as compared with the defective group, the latter shows consistently higher proportions than the former. A probability test, however, indicates that 4 of the 18 possible differences between the proportions are not statistically significant, namely, the differences at ages 6, 9 and 11 years for the boys, and at age 6 for the girls. At these ages, therefore, it cannot be stated that the differences between the physically non-defective and defective groups of this experience with respect to nutritional impairment are not due to chance.

Considering the evidence given above as a whole it is sufficient to indicate that the physically non-defective and the physically defective children differ with respect to nutritional impairment, and with an order of magnitude as given.

Summary. Examination of approximately 30,000 white children, ages 6 through 14 years, of 21 States (representing chiefly the north-

eastern and central regions of the United States) showed that about one-half of the children had one or more recorded physical defects, principally carious teeth, defective tonsils and adenoids.

It is found that 6.5% of the boys with physical defects had a nutritional status that was judged poor or very poor, while the per cent for the physically non-defective is 3.8. The corresponding per cents for the girls are 10.2 and 5.4, respectively. The difference between the per cents for the physically defective and the physically non-defective is statistically significant for both sexes.

The evidence presented is of sufficient weight to indicate that in this experience physical defects (principally carious teeth, defective tonsils and adenoids) are associated with nutritional impairment, and with an order of magnitude as given.

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RIEDEL'S STRUMA.

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IN 1896, Riedel reported 2 cases of a peculiar and hitherto unrecognized disease of the thyroid characterized by extreme induration (eisenhart) and fixation of the gland. At operation, extensive infiltration of the vessels and nerves of the neck seemed to confirm Riedel's diagnosis of malignancy and allowed only a partial resection. The excised tissue showed a chronic inflammation and to Riedel's surprise, both patients not only made an uneventful recovery but subsequently showed complete resolution of the remaining portion of the mass. Within the next few years similar cases were reported by Tailhefer, Berry, Delore and Alamartine and others.

In 1912, Hashimoto published 4 cases resembling Riedel's struma clinically, but histologically showing not the prominent fibrosis characteristic of Riedel's cases but rather a diffuse, lymphocytic infiltration with the formation of lymphoid follicles. Hashimoto regarded this as a new disease and named it "struma lymphomatosa." The relationship of this condition to Riedel's struma has been discussed elsewhere.

The first cases on this continent were reported by Thomas and Webb in 1923, followed by Bohan, St. George, Meeker, Smith and Clute and others. On examination of the reported cases it was found that in many the history was meagre or absent and in some the diagnosis was made on purely clinical grounds. For various reasons it was found that of 187 published cases from 91 sources reported up to July, 1932, all but 82 had to be rejected (Table 1).

TABLE 1.—CASES OF RIEDEL'S STRUMA.

Author.	Date.	Cases.	Acc'd.	Rej'd.	Case No.
Semple	1869	1	..	1	
Woelfler	1883	1	..	1	
Bowlyby	1885	1	1		
Riedel	1896	2	2		
Cordua	1896	1	..	1	
Tailhefer	1896	1	1		
Riedel	1897	1	1		
Tailhefer	1898	5	..	5	
Kuettner	1898	2	1'	1	2'
Loewy and Loeper	1899	1	..	1	
Viannay	1900	1	..	1	
Ricard	1901	1	1		
Walther	1901	2	..	2	
Poirier	1901	1	..	1	
Berger	1901	1	..	1	
Berry	1901	3	1'	2	3'
Poncet	1901	4	..	4	
Ourmanoff	1902	1	..	1	
Genet	1904	1	..	1	
Chalier	1907	1	..	1	
Jaboulay	1907	1	..	1	
Poncet and Leriche	1909	1	1		
Schloffer	1909	1	1		
Silatschek	1910	1	1		
Spannaus	1910	1	1		
Delore and Alamartine	1911	3	1'	2	1'
Barjon	1911	1	..	1	
Schileau	1911	2	..	2	
Hashimoto	1912	4	4		
Meyer	1912	1	1		
Murray and Southam	1912	1	1		
Vogel, R.	1912	1	..	1	
Tomaselli	1913	1	..	1	
Simon	1913	1	1		
Wrede	1914	1	1		
Cavalli	1914	1	..	1	
Heineke	1914	2	2		
Bruenger	1914	3	..	3	
Balfour	1918	1	..	1	
Nicholson	1921	1	..	1	
Kleinsehmidt	1921	1	..	1	
Berry	1921	1	..	1	
Reist	1922	6	3'	3	1' 3' 4'
Erkes	1922	1	1		
Rehn	1922	1	..	1	
Haberer	1922	1	..	1	
Ewing	1922	4	..	4	
Simmonds	1923	20	..	20	
Mysch	1923	1	..	1	
Monod	1923	3	1'	2	1'
Thomas and Webb	1923	1	1		

TABLE 1.—CASES OF RIEDEL'S STRUMA.—(Continued.)

Author.	Date.	Cases.	Acc'd.	Rej'd.	Case No.
Bohan	1924	1	1		
St. George	1924	3	2'	1	2' 3'
Meeker	1925	1	1		
Shaw and Smith	1925	6	4'	2	3' 4' 5' 6'
Hahn	1925	1	..	1	
Smith and Clute	1926	5	5		
Maloney	1926	3	2'	1	2' 3'
Searls and Bartlett	1926	2	..	2	
Gruenberg	1926	1	1		
Manninger	1926	1	..	1	
Agnoli	1926	2	..	2	
Schmincke	1926	1	..	1	
Wegelin	1926	1	..	1	
Payr	1927	5	..	5	
Tucker and Gertz	1927	1	1		
Matthews	1927	1	1		
Schultz	1927	3	..	3	
Perman and Wahlgren	1927	1	1		
Johnson	1928	1	..	1	
Mallet-Guy <i>et al.</i>	1928	1	1		
Wingate	1929	2	2		
Boyd	1929	1	..	1'	
Heyd	1929	2	1	1	
Kent	1929	2	2		
Enderlen	1929	1	1		
Hellner	1929	1	1		
Pluecker	1929	1	1		
Eberts <i>et al.</i>	1929	1	1		
Maloney	1929	3	..	3	
Kreuzbauer	1930	5	1'	4	4'
Austin	1930	2	2		
Vogel	1930	2	2		
Bothe	1931	1	1		
Roulet	1931	3	1'	2	2'
Traum	1931	1	1		
Kreuzbauer	1931	1	1		
Prati	1931	2	1'	1	2'
Graham and McCullagh	1931	4	4		
Diez	1932	2	2		
Joll	1932	8	8		
		187	82	105	

The figures in the right hand column indicate the case number of the accepted case. Cases were rejected for one or more of the following reasons.

1. Incomplete clinical data (49 cases).
2. Diagnosis not confirmed by histologic examination (15 cases).
3. Diagnosis not warranted by clinical or histologic findings (30 cases).
4. Previously published by same or other author (11 cases).

Incidence. An outstanding feature of this disease is its rarity. Riedel thought this to be apparent rather than real, due to its tendency to spontaneous regression. In Table 2 is shown the incidence of the disease in various clinics.

Of the 82 cases under study 72% occurred in women. In Pember-ton's unpublished series of 34 cases there was an 82% female incidence.

The youngest proven published cases were 23 years of age. One

patient in Pemberton's series was 19. The oldest published case was a man aged 78; 60% of the cases occurred in the fourth and fifth decades, 14% in the third and a similar number in the sixth decades.

TABLE 2.—THE INCIDENCE OF RIEDEL'S STRUMA IN PROPORTION TO TOTAL THYROIDECTOMIES.

Author.	Thyroid-ectomies.	Riedel's.	Per cent.
Schloffer	450	1	0.20
Riedel	1,064	3	0.28
Berry	500	1	0.20
Schultz	305	3	0.98
Smith and Clute	1,200	5	0.41
Enderlen	3,396	1	0.03
Jackson	2,000	1	0.05
Eberts <i>et al.</i>	1,050	1	0.10
Frazier	1,551	4	0.26
Pemberton	12,219	34	0.28
Joll	2,000 +	8	0.40
Graham	17,826	27	0.15
Eisen	2,908	7	0.24
	<hr/> 46,469	<hr/> 96	<hr/> 0.20

Etiology and Pathogenesis. The early writers regarded the condition as a fibroma (Bowlby, Ricard), as a type of cirrhosis (Riedel, Tomaselli, Crotti) or as an especially slow-growing form of scirrhous cancer (Poncet, von Eiselsberg). A syphilitic basis for this disease was long maintained (Kuettner, Delore and Alamartine, Monod); in not one of the 82 cases, however, was there any evidence of hues. Until quite recently the condition was regarded by some (Schloffer, Plummer and Broders, Crotti) as tuberculous, but, of late, this view has been largely abandoned. The modern tendencies have been to regard it as a chronic inflammatory process, a granuloma or as an involutionary phenomenon. The granuloma theory was first suggested by Meyer who noted in his case plasma cells and eosinophils, as Hodgkin's disease, but without the characteristic Sternberg cells. This view is shared by Ewing, Meeker and Schultz.

Williamson and Pearse, upon morphologic grounds, regard Riedel's struma as synonymous with "lymph-adenoid goiter." It represents to them a physiologic insufficiency, the lymphocytic reaction being proportional to the failure of the hyperplastic effort. This view does not explain the characteristic extrathyroid involvement associated with Riedel's struma, so that Joll restricts this pathogenesis to those cases of the "Hashimoto type" without extracapsular extension.

The inflammation theory is based upon the obvious fact that both clinically and pathologically the disease presents many of the characteristics of an inflammatory process. As opposed to this hypothesis, however, it has been pointed out (Marine, von Werdt) that too much importance should not be assigned to the presence of

lymphocytes and fibrous tissue since these may not have the same significance in the thyroid as elsewhere in the body. Marine regards their proliferation as part of the general thyroid reaction during active hyperplasia (see Williamson and Pearse, Joll).

Since thyroiditis is never primary (Kocher, Marine) foci of infection have been sought in the teeth (Bohan) and in the pharynx and tonsils (Monod, Meeker, Kocher, Kent, Searls and Bartlett). The causative agent has been thought to be the staphylococcus (Tailhefer), *Streptococcus viridans* (Searls and Bartlett), rheumatism (Vogel, Simmonds), influenza (Erkes, Wegelin, Redner) and a leptothrix (Meeker).

A history of pre-existing goiter was found in 37% of the cases. In 4 of my own there were associated adenomata, but these clearly did not enter into the pathologic picture.

Ewing's views as to the unity of Hashimoto's struma and Riedel's struma were challenged by Perman and Wahlgren and, more recently, by Graham who regards Hashimoto's struma as an involutional disease with local symptoms in the thyroid. Riedel's struma he believes to be a local condition with general manifestations only insofar as might result from the strategic position of the thyroid. This subject has been discussed at length in a previous paper.

Symptomatology. The outstanding symptom present in all cases was a swelling in the neck. Dyspnea on exertion was present in about half of the cases. Dysphonia and mild hyperthyroid symptoms were present in between 25 and 30% of the cases. Pain and dysphagia were found in less than 20% of the cases. About 20% complained of a "choking feeling." The latter is probably mechanical in nature and is characteristically associated with suffocative attacks in bed. The pain is present in the mass itself and radiates up to the ear or down to the shoulders or chest. The duration of the symptoms averaged 10 months.

Examination. The general appearance was that of a patient with a goiter of slight activity. The average temperature was 98.5, pulse 90, respiratory rate 20 and blood pressure 130/82. The condition was unilateral in 40%. The size of the mass, as determined by clinical examination, varied from that of a hazel-nut to that of an orange. In 3 cases there was substernal extension. There was in all cases a marked induration. In $\frac{1}{2}$ of the cases there was a decrease in mobility down to complete fixation.

The lymph nodes were uninvolved. The skin was not altered or adherent. Suppuration was absent. The trachea was compressed or deviated in 16 cases. Vocal cord paralysis was found in 1 reported case and in 4 of Pemberton's series.

The average pre-operative B.M.R. was +10. The hemoglobin averaged 82% and the red cell count 4,746,000. The average white cell count was 8900 with a normal differential count. Serologic tests

for syphilis and tuberculosis were negative. The blood chemistry was normal.

Differential Diagnosis. In 66% of the cases the clinical diagnosis was some form of malignancy. A correct pre-operative diagnosis of Riedel's struma was made in only 5 cases. In the differential diagnosis one must consider cancer, infection, tuberculosis and syphilis of the thyroid, actinomyces and woody phlegmon of the neck.

According to Crile cancer occurs in about 2% of thyroidectomies—about 10 times more frequently than does Riedel's struma. The incidence is greatest in patients over 45. In 90% of the cases (Dinsmore) the malignant process becomes engrafted upon a pre-existing adenoma. Growth is apt to be progressive. Rapid growth with general good health favors the diagnosis of Riedel's disease. In cancer, involvement of the regional lymphatics is the rule and the skin is apt to be attached to the mass. These findings are not present in Riedel's struma. Pain is more frequent in cancer; so is dysphagia (Murray and Southam, Bohan). In cancer, the surface is apt to be nodular; in Riedel's disease, it is smooth. Cancer is apt to be associated with interference with circulation; Riedel's struma, even in the presence of a large tumor (Reist) is not.

Infectious thyroiditis is due to a focus of infection most often, according to Kocher, in the gastro-intestinal tract. A history of recent infection is, therefore, in favor of thyroiditis. In this condition, moreover, hyperthyroid symptoms are apt to be more prominent, the gland is not so hard and extensive adhesions are not likely to be present. The large vessels are pushed aside rather than infiltrated as in Riedel's struma. Redness, tenderness, adhesions to the skin, the presence of pus or of any evidence of a constitutional reaction such as fever or leukocytosis are in favor of infectious thyroiditis and exclude Riedel's disease.

Tuberculosis may occur in the thyroid in a hypertrophic form with a solid gland rapidly growing in size and infiltrating the surrounding tissues. The mass is hard and sensitive on pressure. Adhesions are numerous but not very firm. Lymph node involvement is the rule. There may be a slight temperature and the condition is more apt to be associated with hyperthyroidism than is Riedel's struma. Occasionally there may be an abscess which ruptures through the skin. Postoperative hyperthyroidism is rare in contradistinction to Riedel's struma. Stigmata of tuberculosis may be found on general examination.

The gumma, which is the form of syphilis of surgical importance, usually causes only a moderate enlargement. It occurs usually in women between 25 and 45 and in about half of the cases there is a previous history of goiter. It can be differentiated from Riedel's struma by the following characteristics. The skin is frequently reddened and usually tender. The surface of the mass is usually

soft and occasionally nodular. Fixation is rare. The regional lymph nodes are enlarged and there is a tendency for the mass to suppurate. Constitutional evidences of syphilis should be sought in the patient's history and by the employment of serologic tests.

Woody phlegmon of the neck is a chronic condition found in men in middle life in a depreciated state of health. There is usually antecedent infection of the mouth, pharynx or salivary glands. The mass is very hard and the overlying skin wine-colored and adherent. The general tendency is toward recovery but fatalities may occur through edema of the larynx, pressure or exhaustion.

Actinomyces of the thyroid is characterized, in its early stages, by a boardlike induration of the neck with a typical discoloration of the skin. Later there is softening and ultimately sinus formation with the discharge of characteristic yellow granules.

Treatment. Riedel's opinion that the condition is self-limited has been supported by some modern writers (Manninger, Sloan). The majority, however, favor some form of treatment.

Various medicaments have been tried without any definite benefit. Good results have been reported following radiotherapy (Delore and Alamartine, Crile, Ewing) particularly postoperative radiation (Payr, Ewing, Hellner). Of 8 patients that had received Roentgen ray treatment, 4 showed definite improvement (Silatschek, Heineke, Hellner, Schloffer).

In the surgical management of the disease it has been observed that removal of only a small section characteristically results in the subsequent complete disappearance of the swelling. Riedel believed that the operation in itself initiated a curative process, an effect compared by some writers to that in tuberculous peritonitis. Demonstrable at operation, which they serve to complicate, are dense adhesions between the thyroid and other structures of the front of the neck. In about 60% of the cases these were sufficiently dense to hamper the operative procedure. The capsule was involved in 40%; the carotid sheath in 35%. The trachea was compressed or deviated in over 40% of the cases; the esophagus in only 10%. In about half of the cases a partial resection was done; in about one-third a subtotal resection. The remaining cases had a single lobectomy or a biopsy. The actual amount of tissue removed averaged about 90 gm. Four cases required a tracheotomy.

Results and Prognosis. In 62 cases in which sufficient data are supplied for the results to be evaluated 11 (18%) were cured; 37 (60%) were improved; 4 (6%) died, and in 10 (16%) the condition recurred. Under "cured" are included those cases wherein there was a disappearance of the tumor with relief from all associated symptoms with no postoperative complications. Practically the same results were obtained irrespective of the surgical procedure or the amount of tissue excised.

Postoperative hypothyroidism was found in 43% of the reported

cases and in 68% of Pemberton's series. The tendency to the development of hypothyroidism was found to be proportional to the amount of tissue resected. In at least 2 cases definite hypothyroidism was found before operation. Undoubtedly the disease process itself is a potent factor in its production. The average postoperative basal metabolism was -10 .

Of the 10 patients that had recurrence 6 were subjected to a second operation from 6 months to 2 years after the first. In 5, a permanent cure resulted, while in 1, the residual tumor did not disappear until after removal of a focus of infection in the patient's teeth. The amount of tissue excised did not appear to be the determining factor in the recurrence since these patients were, on the whole, submitted to the same operative procedures as those that did not develop a recurrence.

Pathologic Anatomy. The amount of involvement varied from a pea-sized nodule (Bothe) to extensive infiltration of the vessels of the neck to the base of the skull and down into the mediastinum (Bowlby, Berry, Meyer, Tailhefer). The surface of the mass is usually smooth. The color may be yellowish, gray or pink. The consistency has been compared to wood (woody thyroiditis), bone, stone and iron (Riedel). On section it cuts like cartilage and the mass creaks under the knife. The cut surface is fibrous in appearance. The capsule is usually thickened. The normal lobulations may be completely destroyed. The regional lymph nodes are not involved.

Microscopically, there is an infiltration with round cells and fibroblasts and adult fibrous tissue choking off the remaining thyroid cells into isolated islands. There may be pseudo-giant cells and enlarged thyroid cells arranged into fetal-looking acini. Hashimoto's and Meyer's findings have already been mentioned. Meeker's finding of the remains of the postbranchial body and its duct within the mass have not been duplicated. Shaw and Smith observed frequent mitoses in the cells of the fetal alveoli and fibrous replacement of the round cells. They noted also a tendency to fibrosis in the secondary centers of the lymphoid follicles, a finding that I can confirm.

Case Reports. CASE 1.—Mrs. L. B., aged 56, admitted September 22, 1925, complained of a swelling of the neck and nervousness of 6 years' duration. During this time she had put on 45 pounds in weight. Three years ago she became dyspneic on exertion and the lump began to grow rapidly, associated with difficulty in swallowing. General examination was negative. Her pulse was 84 and blood pressure 145/84. There was a firm, non-tender, nodular mass in the right lobe of the thyroid and the isthmus, which moved on swallowing. The clinical diagnosis was adenomatous goiter. At operation on the following day, the isthmus and both lobes were resected without undue difficulty. The postoperative course was uneventful and the patient was discharged on the 18th day. Two months after the operation she showed clinical evidences of hypothyroidism with a B.M.R. of -21 , for which she

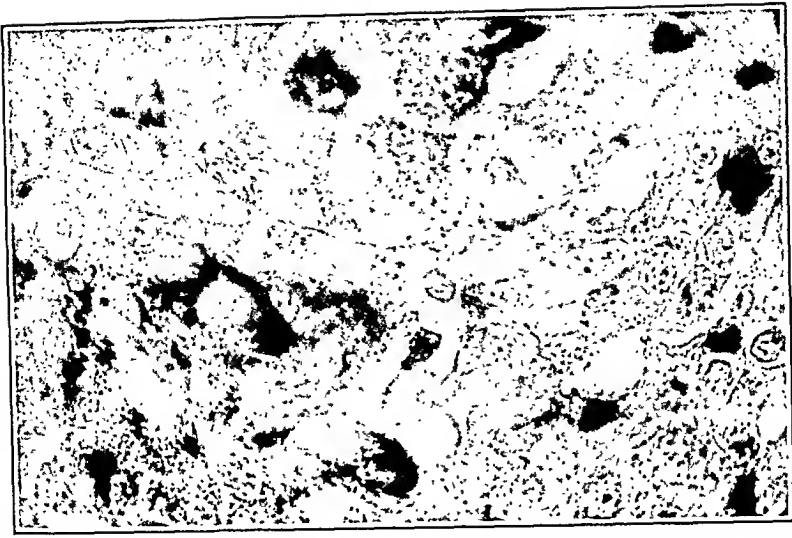


FIG. 1.—(Case 1.) Mitochondria. The active new epithelial cells contain many mitochondrial granules. The degenerated cells contain none.



FIG. 2.—(Case 2.) Acinar colloid and its contained cells. The latter show phagocytosed colloid particles. The colloid shows numerous vacuoles.

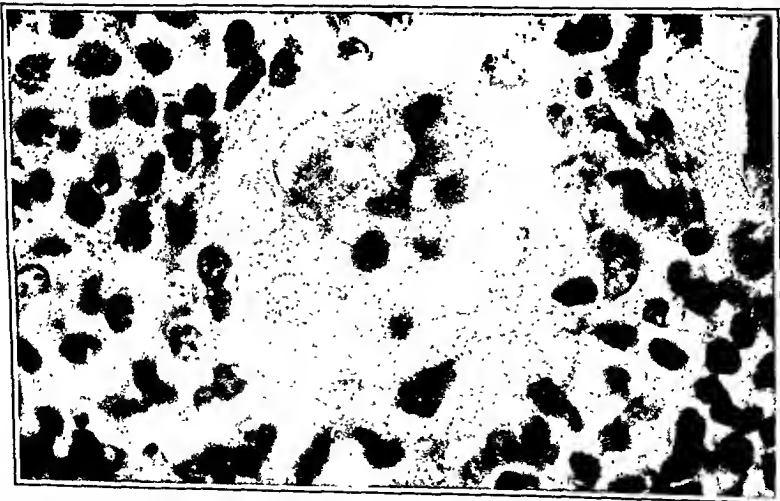


FIG. 3.—(Case 2.) Round-cell infiltration about an acinus, the lining cells of which are undergoing hydropic degeneration.



FIG. 4.—(Case 4.) Young fibrous tissue with fibroblasts replacing a round-cell infiltration. The acinar cells have disappeared in some alveoli. In others it is in the process of undergoing hydropic degeneration.



FIG. 5.—(Case 4.) An acinus, the lining epithelial cells of which have been completely replaced by fibrous tissue. The colloid content is largely composed of lymphocytes and endothelial cells.



FIG. 6.—(Case 4.) Pseudo giant cell of colloid type within an alveolus.

was given thyroid extract grains 3 per day. On March 17, 1933, she felt well and showed, on examination, no sign of recurrence.

Pathologic Examination. The capsule is thin and the gland firm and friable. On section it is homogeneous and pinkish-gray in color and is divided into uneven lobes by fibrous septa springing from the capsule.

Microscopically, the epithelium is arranged in small, round acini most of which contain colloid, in strands, small, irregular nests or isolated cells. The cells are larger than normal with a vesicular nucleus and a prominent nucleolus. The cytoplasm is granular. The epithelial cells are degenerated, either in the hydropic form with final rupture of the cell wall and extrusion of the cytoplasm into the acinus, or in the pyknotic form with fragmentation of the nucleus, its extrusion and ultimate phagocytosis. Completely degenerated epithelial cells are replaced by round cells. Enmeshed within the acinar colloid can be seen desquamated acinar cells, lymphocytes, plasma cells and, more rarely, polymorphs, fibroblasts and mononuclears. Some of these cells show a halo of phagocytized colloid about them.

The cellular infiltration consists chiefly of small lymphocytes, epithelioid cells and a varying number of plasma cells. Polymorphs are infrequent. The lymphocytes occur as a diffuse infiltration and as aggregated follicles, most of which show secondary centers with a border of one or two rows of epithelioid cells and a thin-walled bloodvessel in the center. Also present are reticulum cells and lymphoblasts, the latter showing frequent mitotic figures. Pseudo giant cells are frequent and appear to be formed of a mass of colloid with desquamated epithelial cells arranged about its periphery.

Fibrous tissue is not prominent and consists mostly of young collagen fibrils with numerous fibroblasts. The fibrils are frequently hyalin and appear to spring from the septa that extend from the capsule. They ramify into small divisions which infiltrate between the alveoli and the cell nests. The vascularity does not appear increased. There is a slight thickening of the intima and slight periarterial fibrosis.

CASE 2.—Mrs. M. S., aged 49, was first seen on May 23, 1929. Her illness began 5 months previously with loss of appetite and weight (15 pounds), fatigability, dyspnea and palpitation on exertion. On examination her pulse was 100 and blood pressure 110/78. General examination was negative. The neck showed a firm enlargement of the right lobe of the thyroid and the isthmus. There was a slight thrill over each superior pole. The clinical diagnosis was Graves' disease. At operation, on the day following admission, the gland was found to be strikingly hard, suggesting carcinoma. No lymph nodes were palpable. The subcutaneous tissues were of a gummy, leathery character. The perithyroid muscles were firmly stuck to the gland which was friable and difficult to clamp. Both lobes and isthmus were resected. On March 17, 1933, the patient had no complaints except for a tired feeling and no objective signs of recurrence. A slight hypothyroidism (B.M.R., -10) was under control with thyroid extract gr. i per day.

Pathologic Examination. The tissue is firm and inelastic, with a smooth, rounded surface with a thin capsule. The cut surface is opaque and whitish with a marked increase in connective tissue.

Microscopically, the involved areas show proliferation of the interstitial cells with the formation of immature follicles. These cells are larger than normal and have an oval, brightly staining nucleus and occasionally show evidences of degeneration. The process is more advanced than in Case 1 as evidenced by the presence of acini lined with fibrous tissue only. Pseudo-giant cells of the colloid type are present. The outstanding characteristic is the large amount of fibrous tissue, which is present in bands which seem to surround and choke off groups of epithelial cells and follicles. Occasionally it is seen in the process of replacing the round cells which are of the

same type and in the same proportion as in Case 1. The bloodvessels, however, show a more advanced intimal thickening and periarterial fibrosis.

CASE 3.—Mr. W. G., aged 42, was admitted on November 12, 1930. About 2 years previously he began to lose strength, appetite and weight (45 pounds in 2 months!) followed by prominence of the eyes and other hyperthyroid symptoms. There was a temporary improvement with the use of Lugol's solution, followed by a relapse. On examination the pulse was 108 and the blood-pressure 128/80. The patient showed the general findings and eye signs of Graves' disease. The thyroid felt grossly lobulated and finely granular. It was markedly hard and adherent to the underlying tissues. Each lobe was about the size of a turkey egg. There were no thrills or bruits. At operation, 2 days later, the enlarged lobes and isthmus felt hard and lumpy. There was a large amount of colloid. There was a calcified adenoma at the left lower pole. On August 1, 1932, this patient had no complaints and showed no evidences of recurrence.

Pathologic Examination. The capsule is thin and the surface pinkish and semitranslucent. On section there is a very marked diffuse increase in scar tissue throughout the lobe.

Microscopically, there is to be seen a thick, compact, fibrous connective-tissue stroma including small islands of medium-sized acini which show a moderate hyperplasia. The fibrous tissue appears to be old and shows, in some areas, a moderate small round-cell infiltration. There is some increased lymphoid deposit. There is evidence of degeneration and atrophy of the acinar cells, and also, apparently of the newly-formed large epithelial cells arranged in clusters or in small, round acini.

CASE 4.—Mrs. F. F., aged 56, sought advice on May 12, 1931, because of a swelling in the neck associated with headache, loss of appetite, insomnia and palpitation of 2 months' duration. Later there was dysphagia and the usual symptoms of hyperthyroidism. Her pulse was 80 and the blood pressure 144/90. General examination was negative except for poor teeth. Both lobes of the thyroid were hard and tender. No definite thrills or bruits. The clinical diagnosis was exophthalmic goiter. At operation 1 week later the ribbon muscles were found to be fused with the gland substance which latter presented a whitish, sclerotic appearance. As Riedel's struma was suggested, the usual radical procedure was not followed. About one-half of the right and one-third of the left lobe were resected. The trachea was exposed and freed to prevent future compression. The patient developed a mild hypothyroidism 6 months after operation (B.M.R. -7) which was corrected with thyroid extract (gr. i per day). On January 24, 1933, she reported a return of all her symptoms although there was no objective evidence of recurrence.

Pathologic Examination. Both lobes are grayish in color, somewhat mottled with small hemorrhagic spots. The capsule is smooth but markedly thickened. Consistency is firm and mildly elastic. The cut surface is yellowish and mottled, and shows large bands of scar tissue radiating in all directions from the capsule. In the lower portion of the right lobe there is a fetal adenoma measuring 0.5 cm. in diameter.

Microscopically, the epithelium in the involved areas is seen to be in the form of young follicles with or without a lumen; with less frequency, hyperplastic alveoli are to be seen. Hydropic degeneration with karyolysis is seen everywhere. In the early stages of this process disappearance of the individual cell outlines of an acinus gives the impression of an alveolus lined by a syncytial mass of epithelium. The same process in an epithelial cell cluster leads to the formation of one type of pseudo giant cell. Occasionally a true Langhans foreign-body giant cell is seen. The cellular infiltration is of about the same character as in the previous cases. Fibrous

tissue replacement is active and is evident as richly-nucleated collagen fibrils ramifying between the alveoli and cells.

CASE 5.—Mrs. I. Y., aged 54, was seen on December 4, 1930, because of a choking feeling associated with weakness and fatigue. Her symptoms began 8 months previously with pains in the left shoulder and arm, extending upward to the mastoid. She felt tired and weak and occasionally breathless. Her pulse was 80 and the blood pressure 154/100. On examination the face was pale and somewhat puffy. The thyroid was enlarged, firm and lobulated and, in the course of the next 6 months, it became strikingly hard. The B.M.R. was -21 . Four months later she became hoarse. The clinical diagnosis rested between Riedel's struma and carcinoma. At operation, on October 29, 1931, the thyroid appeared pinkish-white and hard. The capsule was much thickened. The isthmus and both lobes were excised. Seven months after operation the patient developed a hypothyroidism with a B.M.R. of -28 which was corrected with thyroid extract (gr. iv per day). On March 23, 1933, the patient complained only of a slight dyspnea on exertion. Her pulse was 90 and blood pressure 170/104 and her B.M.R. -4 . There was no sign of recurrence.

Pathologic Examination. The tissue is firm and almost cartilaginous in consistency. On section, there is a diffuse, well-marked infiltration with scar tissue and a well-encapsulated adenoma at the left upper pole.

Microscopically, the lesion is less diffuse than in the previous cases. The involved portions are traversed by bands of fibrous tissue rather richly nucleated. Enmeshed in these are groups of alveoli and occasionally pseudo giant cells containing many nuclei. There is evident hyperplasia of the acinar and interstitial epithelial cells. Nuclear remains are scattered about. Fibrosis is the prominent element in the picture.

CASE 6.—Mrs. A. S. M., aged 38, was seen on January 24, 1933, complaining of a lump in the throat associated with hyperthyroid symptoms for the past 15 years but aggravated in the past 3 months following the removal of teeth. Her pulse was 82 and the blood pressure 130/70. There was advanced pyorrhea. There was a fine tremor of the fingers. The thyroid was slightly enlarged and finely lobulated. Two adenomata could be felt in the left lobe. There were mild pulses at the poles. The clinical diagnosis was adenomatous goiter. At operation on February 17, 1933, there was found adhesions between the capsule and the perithyroid muscles. A bilateral resection was done. The patient was discharged 10 days after operation with a B.M.R. of -14 . One month later she complained of a lump in the throat and pains in the left side of the neck radiating to the temple and down the left arm.

Pathologic Examination. The tissue is firm, rubbery and pinkish in color. On section, it shows an unusually marked scar tissue infiltration with little gross evidence of hyperplasia.

Microscopically, in the lightly involved areas there was a definite hyperplasia of the interstitial cells resembling, in many areas, the picture of diffuse adenomatosis (Goetsch). Elsewhere there were large epithelial cells occasionally showing degeneration. The colloid frequently showed numbers of cells enmeshed within it. The round cells are proliferated diffusely and are also aggregated into follicles with germinal centers. The latter differ from those seen in Case 1 in being irregular in shape and much larger compared to the size of the follicle. They are also not surrounded by such regular, concentric layers of endothelial cells. Frequently there appears to be a central necrosis within such a germinal center. There are no true giant cells and one pseudo giant cell is noted. There is a large amount of fibrous tissue and the vascularity is increased slightly. The appearance is similar to that in Case 1 but in a more advanced state.

CASE 7.—Mrs. E. J., aged 51, was admitted May 5, 1933. She had had a goiter for the last 28 years, associated, in the past 15 years, with nervousness, dizzy spells and indigestion. Six months previous to admission she began to have definite hyperthyroid symptoms and 4 months later she noticed that the goiter had extended across the midline from the right to the left side. With this was associated pain in the back of the neck radiating up to both ears. The pulse was 88 and the blood pressure 160/84. There was slight prominence and lid lag in both eyes. The heart showed an apical systolic murmur. Both lobes were nodular and very hard. The clinical diagnosis was adenomatous goiter. At operation, on May 17, 1933, the pre-thyroid muscles were found to be adherent to the gland which was grayish-white in color, moderately enlarged and very hard. Both lobes were fused over the midline forming a single hard mass. The trachea was exposed with some difficulty. The condition was recognized as Riedel's struma, hence a very conservative resection was done with removal of only 50% of the gland to guard against hypothyroidism. The patient was discharged 10 days after operation with a B.M.R. of +4 and feeling slightly improved.

Pathologic Examination. Both lobes are firm and inelastic. The capsule is thickened. On section, there is a very marked infiltration with scar tissue, between the bands of which are relatively small areas of thyroid tissue, containing very little macroscopic acini and colloid.

Microscopically, there is a very marked infiltration with scar tissue which is extensively infiltrated with lymphocytes. The latter are collected into small follicles which occasionally possess a germinal center. There is an increased amount of thyroid gland structure composed of hypertrophic epithelial cells which are occasionally found in small lobules and in other instances as isolated acini. The latter are small, regular in outline, filled with colloid and lined with flattened cells. The bloodvessels show considerable thickening of their coats.

Mitochondrial Studies. Goetsch has demonstrated that activity in thyroid epithelium can be gauged by a study of the mitochondrial content of the cytoplasm. This seems to the writer to present an accurate method of definitely establishing the significance of the hypertrophic epithelial cells characteristic of Riedel's struma. Studies were made upon Cases 1 and 5. The technique was that of Cowdry.

The mitochondria in both cases were of the "rod" type. In Case 1, in which no preoperative iodine had been administered, the cells of the older thyroid acini and the new hypertrophied cells were found densely packed with the reddish granules. The cells which were undergoing degeneration showed few or no granules but rather larger black droplets of fat. In Case 5, in which pre-operative iodine had been administered, practically no mitochondria were found.

I interpret these apparently paradoxical findings as follows: The results in Case 1 indicate a profound activity in the hyperplastic and hypertrophied new epithelium and doubtless represent an effort at compensation for destruction of the older alveoli. The lack of mitochondria in Case 5 is due, I believe, to the fact that the iodine, even in the small quantities administered, was sufficient to inactivate the epithelial cells to the degree indicated by the findings.

Discussion. We may now attempt to reconstruct the various changes that take place in Riedel's struma. We do not know whether the round-cell infiltration is primary and causes the degenerative changes in the epithelial cells; or whether, on the other hand, this infiltration, together with the degenerative changes, are both brought about by the same noxus. In any case, the first anatomical changes to be noticed are the infiltration throughout the gland of lymphocytes, plasma cells, endothelial cells, and a small number of polymorphs and fibroblasts, accompanied by degenerative changes in the epithelium. These are usually of a hydropic type with karyolysis. Less often there are pyknotic changes in the nucleus with karyorrhexis. In either case, there is anatomic replacement of these degenerated epithelial cells by round cells. Functional replacement is represented by hyperplastic changes in the old alveoli and by the formation of new hypertrophied epithelial cells arranged in clusters, or in fetal looking alveoli. That these new cells are active is indicated by mitochondrial studies.

During this time, a proliferation of fibrous tissue throughout the gland forms bands which extend as septa from the capsule and divide the lobe into smaller and smaller lobules ultimately forming fine branches which infiltrate between the alveoli and the interstitial cells. Gradually they replace the round cells, so that finally the acini are lined by fibrous tissue only. In a similar manner, fibrous tissue replacement takes place within the germinal centers, which seem more prone to this fibrosis than the rest of the lymphoid follicle. With increasing fibrosis, the acini are squeezed into odd, linear, shapes. At this stage true Langhans giant cells have been seen.

Degeneration and functional replacement of epithelium do not continue indefinitely. In the course of time either of two eventualities may happen. The original noxus may cease to be active so that the degenerative process may slow down until a condition of equilibrium is attained. On the other hand, the noxus may continue to act until there sets in, ultimately, an exhaustion of the epithelium which is then replaced anatomically only by round cells and finally by fibroblasts. In the former eventuality which, as in Riedel's Case 3, may set in many years after the commencement of the disease, a clinical cure will result. In the latter process of events the case goes on to myxedema.

The presence of adenomata in the affected glands seems to be a coincidental finding only since in none of the 4 cases in our series in which this occurred was the adenoma in any way involved in the disease process.

Summary. An analysis is presented of 82 cases of Riedel's struma, representing all the acceptable cases that could be found after an exhaustive search of the literature up to July, 1932. In addition statistics as to the incidence of the disease are presented

on 46,317 thyroidectomies. I report also 7 hitherto unpublished cases. On the basis of an analysis of the above material the following facts may be regarded as established.

Riedel's struma occurs in 0.20% of thyroidectomies and 3 times as frequently in women as in men. In both sexes it is found usually in the fifth decade, the average age being 44.

The outstanding theories as to its pathogenesis are that it is a primary thyroiditis, a benign form of granuloma, or that it represents a faulty involution of the thyroid.

The outstanding symptoms are the presence of a mass in the neck, dyspnea on exertion, voice changes, mild hyperthyroid symptoms and less frequently, pain and dysphagia.

The gland may be symmetrically enlarged or the disease may affect one lobe only. The size of the involved area varies from that of a pea to a large mass extending along the vessels of the neck from the base of the skull downward into the mediastinum. The lesion characteristically shows induration of various degrees. The surface is more often smooth than nodular. About one-half of the cases show fixation of the gland. There is no involvement of the regional lymph nodes. The skin is neither reddened, tender, nor adherent to the mass. Suppuration never occurs. Evidences of interference with circulation are not found.

The average pre-operative B.M.R. is +10; postoperative -10. There may be a slight anemia, otherwise the various tests of the blood and urine are negative.

The disease must be differentiated from malignancy, infectious thyroiditis, tuberculosis and syphilis of the thyroid, actinomyces and woody phlegmon of the neck. Of the reported cases 66% had been misdiagnosed as malignancy. Most of the remainder were thought to be adenomatous goiter. Only 6 of the reported cases were correctly diagnosed clinically.

Medical treatment is of no value. Radiotherapy has been thought effective in some cases, presumably early cases with lymphocytic infiltration. There is evidence that the disease is self-limited and tends to spontaneous recovery with hypothyroidism. The usual treatment is surgical, but in the absence of pressure symptoms its indication is questionable. The procedures usually recommended are section of the isthmus to relieve present or future compression of the trachea with a partial bilateral resection leaving more than the usual stumps. Complications have occurred and operative mortalities are on record but usually in the older cases where too much surgery was attempted.

The prognosis for improvement is good. There is more than a 10% chance for recurrence. Hypothyroidism develops in the majority of the operated cases. Neither cure, recurrence nor hypothyroidism develop in direct proportion to the amount of tissue resected.

The pathology of the condition is that of a degeneration and atrophy of the epithelium with compensatory hyperplasia and hyper-

trophy, followed by round-cell infiltration, and ultimately, by fibrous tissue replacement. Extrathyroid involvement is found in the advanced cases. The pathogenesis of the condition is not definitely understood.

The cases reported are from the services of Drs. Emil and Arthur Goetsch at the Long Island College Hospital of Brooklyn, N. Y., both of whom I desire to thank for the use of their material. I also wish to acknowledge with thanks personal communications from Drs. Lahey, Jackson, Pemberton, Frazier and Graham as to their experience with the disease.

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EOSINOPHILIA AND SKIN TESTS IN THE DIAGNOSIS OF TRICHINOSIS.

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IN 1933 an outbreak of trichinosis occurring in Atlantic City¹ provided an opportunity to study in 33 of those exposed to the disease the results of the intradermal reaction originated by Bachman.² From this study it was concluded that, as the demonstration of eosinophilia was a technically simple procedure always available to and readily applied by the clinician, whereas the intradermal test required an antigen somewhat difficult to prepare and not readily available, the skin test presented no marked practical advantages over the demonstration of eosinophilia.

This conclusion was later attacked by Friedländer³ on the grounds that: *a*, conclusions concerning the value of the skin test in trichinosis could not be based upon the test when conducted according to the method described by Bachman;⁴ *b*, other investigators, including himself and his associates, had found the intradermal reaction, when employed with various antigen dilutions in order to rule out non-specific protein sensitivity, to be of great value in the diagnosis of trichinosis; and, finally, *c*, because eosinophilia occurs in other diseases. In subsequent discussions by other workers, to which reference will later be made, both the original paper and Friedländer's comments were noted, the latter with somewhat general approval.

The data which have by now accumulated would seem, however, to warrant some further comment upon the point at issue. Both Friedländer, and those who have to some extent agreed with him, appear to have overlooked factors somewhat pertinent to the issue which I conceive to be, not particularly the value of the skin test as an aid in the diagnosis of trichinosis but the relative value of the skin reaction and the demonstration of eosinophilia in the clinical study of this disease. And I further consider the relative value of any procedure applicable to diagnosis to be somewhat directly influenced by its feasibility.

It can be accepted, I think, that recognition of trichinosis is, first of all, a clinical problem; that the majority of cases will first be seen by the practitioner rather than by clinic personnel or the specialist; and that their recognition by the practitioner will be determined in large part by his clinical acumen aided and reinforced by whatever laboratory procedures are easily and ordinarily available. Nor can the greater difficulties of the skin test be denied, whereas the demonstration of eosinophilia is a simple procedure readily available to any practitioner anywhere at any time. Concerning the relative availability of the two procedures as measures

of ready clinical applicability there would seem to be little question. Concerning their relative efficiency there is room for discussion.

McCoy, Miller, and Friedländer⁵ in a study of the intradermal test conducted with antigen dilutions of 1 to 10,000 or higher report "about 90%" of positive reactions "provided the disease is sufficiently established" (2 to 3 weeks after infection). However, eosinophilia occurs in practically the same proportion of cases and appears at about the same period in the disease (second to third week). Whereas eosinophilia gradually declines after the third or fourth week, the intradermal reaction persists for much longer periods which, however, are those in which, as encystment progresses, the symptoms decline and the disease becomes more a matter of academic interest.

Spink and Augustine⁶ who in the body of their paper agree with the comments of Friedländer, nevertheless state in their summary that "the most reliable aid in these cases was the presence of an eosinophilia."

Drake, Hawkes, and Warren,⁷ also in agreement with Friedländer's comments, report that of 25 individuals showing eosinophilia, half gave negative skin reactions and express the belief that such individuals, though not clinically ill, represent latent cases of trichinosis.

Sobel,⁸ who also quoted Friedländer's criticisms, also comments upon the eosinophilia present in the 7 surviving patients of the 8 in his series and emphasizes in his summary that the intradermal test, though a valuable aid, cannot replace the biopsy in the final and absolute diagnosis of trichinosis.

It is true, of course, that biopsy with the actual demonstration of the trichinae, is the final and absolute diagnostic criterion. But biopsy should be suggested and justified by something in the clinical history and the clinical picture. For this purpose eosinophilia, in the presence of a suggestive history or symptomatology, is of significant import.

Friedländer and others have warned that eosinophilia occurs in diseases other than trichinosis and that eosinophilia may be absent in fulminating cases, which are matters of more or less common knowledge. But no one has maintained or even intimated that the diagnosis of trichinosis should be postulated solely upon the presence or absence of eosinophilia.

Eosinophilia, like the intradermal reaction, is only the expression of a reaction to a stimulus which, indeed, is true of any symptom in any disease.

The intensity of such a reaction, indeed its occurrence, is dependent not solely upon the presence of the stimulus, but preëminently upon the ability of the individual to react, and many reactions following specific stimuli are absent in the presence of fulminating infections, either because the patient is too profoundly overwhelmed

to possess the ability to react, or because sufficient time has not elapsed for the evidences of reaction to appear. On the other hand, the stimulus may be too slight to cause an evident reaction, or this has not yet fully developed, or the patient may not possess the ability to react in any marked degree. There may thus be varied explanations for the absence of positive skin reactions in the latent cases of trichinosis which presented eosinophilia. I have encountered no reports of the skin test in fulminating cases. It is, of course, true that not all cases of trichinosis show an eosinophilia of significant degree, nor even, perhaps, any eosinophilia at all. But neither is the intradermal reaction present in all cases despite which trichinosis may still be present in both instances.

It is also true that not all cases of trichinosis show an eosinophilia of equal intensity any more than all cases show an intradermal reaction of equal intensity. But a sufficient proportion of cases of trichinosis show an eosinophilia sufficiently early in the disease and of sufficient intensity to suggest the possibility of this disease *in the presence of other significant symptoms* and to suggest the advisability of other procedures, among which the biopsy and the skin test may well be numbered.

The latest report on this subject appears to be that of Heathman⁹ who presents not only a rather comprehensive review of the pertinent literature, but also reports the results of skin tests, precipitin tests, and eosinophil counts carried out on the same day on 44 cases.

She used antigen dilutions of 1 to 6,000 and 1 to 500 and observed the reactions for 1 hour following the tests and again 24 hours later. An extensive series of controls was included.

Friedländer, in his comment, called attention to the work of Augustine and Theiler¹⁰ and also the report by himself, and McCoy and Miller⁵ as evidencing the value of the intradermal reaction with various antigen dilutions. The latter report, however, shows only 70% of immediate positive reactions to a 1 to 10,000 dilution and 92% to a 1 to 10,000 and 1 to 500 dilutions. Of still more interest is the occurrence of 9% of positive reactions in a series of 104 controls, 18% of positive reactions in 92 cases infected with *Trichuris trichiura* and 62% of positive reactions in the series when both 1 to 10,000 and 1 to 500 antigen dilutions were used. The conclusions of these authors state that "the test may be a valuable aid" and that "a negative test will probably prove more useful in ruling out the diagnosis of trichinosis than a positive one in establishing it."

As Heathman reviews the literature concerning the occurrence of positive reactions to trichinae antigen in individuals suffering from other parasitic infections, for the sake of brevity this will not again be surveyed here. Some of her other observations are referred to below.

Friedländer,⁵ in his comment, emphasized the importance of immediate reactions and discounted those read at 24 hours,

referring to the report by Maternowska.¹¹ But Maternowska divided the reactions into two phases, one reaching its height 9 hours after injection, and the second in 24 to 38 hours.

Heathman records that "it would seem that precipitins and skin tests occur in quite a high percentage of trichinosis patients but not sufficiently early or regularly, at least in the group studied here, to be of great diagnostic aid." She was unable to duplicate the results reported by Friedländer and his associates or others referred to by him, and her conclusions are so pertinent to the point at issue that they are here quoted in full:

"1. In our hands the intradermal skin test and the precipitin test appear to be of much less value in the laboratory diagnosis of trichinosis than do the eosinophile count, together with muscle biopsy, and the study of the meat suspected of being the source of infection.

"2. Intradermal skin tests and precipitin tests in animals heavily infested with *Trichinellæ* larvæ gave even a lower percentage of positive reactions than that found in human beings. Animals did not tend to develop positive intradermal reactions regularly after being tested a number of times. The intradermal tests in both man and animals are less clear-cut and more difficult to read than a number of other diagnostic intradermal tests.

"3. It would seem very important both from the theoretical and practical standpoint that skin tests in trichinosis be more thoroughly studied."

Summary. The conclusion drawn in the original study commented upon by Friedländer was not that the skin test was without value in the study of trichinosis, but that it presented "no practical advantage over the demonstration of eosinophilia." This conclusion might have been better expressed "no practical *clinical* advantage," for, as has been stated, trichinosis is primarily a clinical problem.

The point originally made was that because of its simplicity, reliability, and ready availability the demonstration of eosinophilia was more practical and more practically valuable to the clinician than the intradermal reaction in the *clinical* study of this disease. This conclusion which does not yet seem to have been controverted by subsequent published reports, does not indicate that further laboratory tests should not be used in suspicious cases.

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CYSTOMETRIC STUDIES: THE VALUE OF FOLLOW-UP EXAMINATIONS.

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CYSTOMETRY studies the functional state of the urinary bladder by means of measurement of its capacity at various pressures. By means of the cystometer one obtains three factors: (a) first desire to void (Δ), (b) pressure curve, (c) the maximal voluntary pressure. The factors of a normal bladder are: First desire to void 150 to 250 cc., the pressure curve is gradually ascending and the maximal pressure is 40 to 60 mm. In the hypertonic bladder the factors are altered: First desire is under 150 cc., the curve is very acute, and the maximal voluntary pressure is over 60 mm. In the hypotonic bladder it is just the opposite: First desire to void is above 250 cc., the curve is flat, and the maximal voluntary pressure is under 40 mm. Alteration of at least two factors is characteristic for a neurogenic bladder. In doing cystometric work, we are frequently requested to repeat the cystometrographic reading at different intervals to ascertain the advancement or regression of the disease. In the normal, we are impressed with the constancy of the cystometric data obtained over a period of many months. This constancy of repeated cystometrograms definitely proves the existence of a constant physiologic rhythm in the function of the urinary bladder. In many instances a repeated cystometrogram was actually identical with mathematical accuracy with the one taken a long time previously or would vary only slightly and insignificantly.

Figure 1 shows two cystometric readings in a patient with chronic prostatitis. The one taken 6 weeks later is practically identical with the first.

We therefore regard the cystometrogram as a composite picture of balanced normal bladder function, constant in character and subjectively unalterable (Figs. 2 and 3).

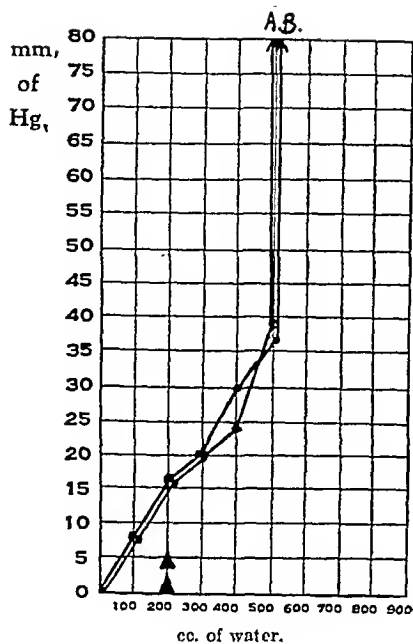


FIG. 1

FIG. 1.—Chronic prostatitis. Cystometrograms taken 6 weeks apart. Both normal (slightly hypertonic) and similar. No change. In this and subsequent figures the solid triangle represents the first desire to void. (W. S., Mt. Sinai, 30-4890.)

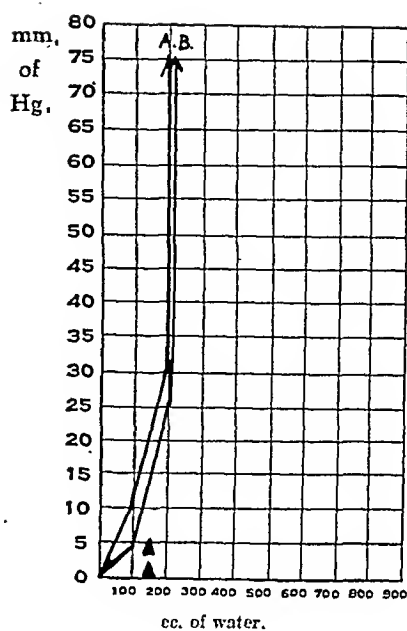


FIG. 2

FIG. 2.—Prostatic uropathy. Cystometrograms indicative of hypertonic detrusor (muscular) taken 18 months apart. No change. (W. R., Mt. Sinai.)

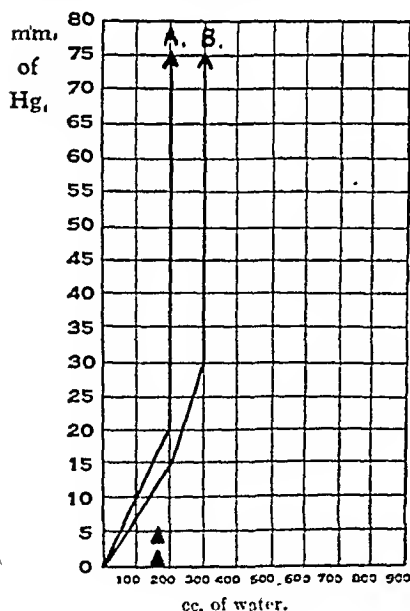


FIG. 3

FIG. 3.—Traumatic cord injury with resulting sclerosis of vessels. Cystometrograms taken 2 years apart. No change. (S. H., Mt. Sinai, Nos. 68636 and 83225.)

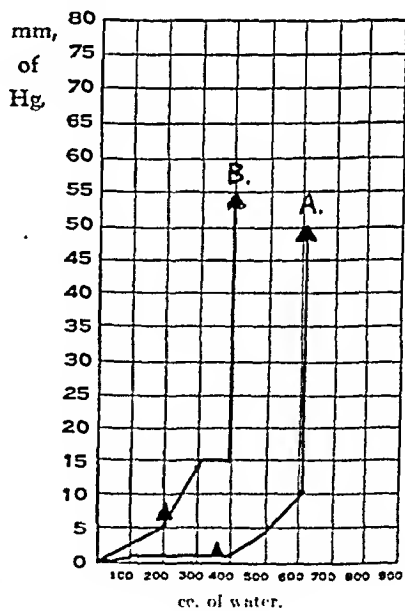


FIG. 4

FIG. 4.—Extradural sarcoma of the spine. Cystometrograms A (before operation). Neurogenic bladder of hypotonic type. Cystometrograms B (after operation). Normal bladder 5 days later. Catheter removed, patient voiding. (N. S., Mt. Sinai, No. 88646, Neurosurgical Service of Dr. F. Grant.)

If one therefore in repeating a cystometrogram finds altered data it can only indicate one thing, namely, true changes in the physiologic rhythm, caused by advancement or regression of the primary disease.

The importance of follow-up studies in a neurogenic bladder can thus not be underestimated clinically—it frequently guides the clinician to undertake or abstain from certain procedures contemplated.

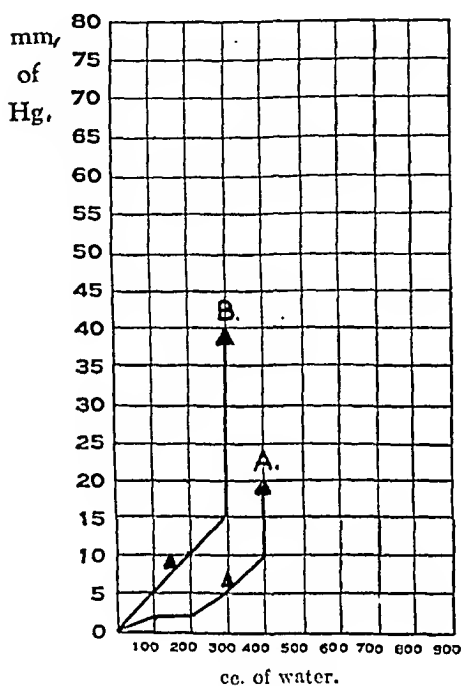


FIG. 5

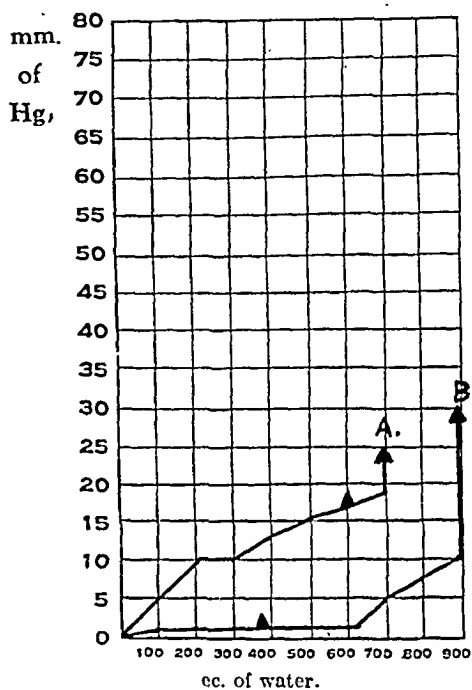


FIG. 6

FIG. 5.—Fracture dislocation of twelfth dorsal vertebrae with cord involvement. Expectant treatment. A, taken May 18, 1935 and B, taken May 25, 1935. Note great improvement in 1 week. While actual urination was not reestablished at the end of the week, the improvement shown by the cystometer greatly influenced us to treat expectantly. Complete recovery. (J. H., Mt. Sinai, 18 years, No. 92078, Orthopedic Service of Dr. M. B. Cooperman.)

FIG. 6.—Tabes dorsalis. Cystometrogram A (August 8, 1934): Neurogenic hypotonic bladder. Cystometrogram B (April 13, 1935): Neurogenic hypotonic bladder. No improvement in spite of antiluetic therapy. (S. B., Mt. Sinai, No. 33-7443, Out-patient Dermat. Service of Dr. S. Greenbaum.)

The value of follow-up repeated cystometrograms is especially valuable in neurosurgical work—on the brain or spinal cord when an indwelling catheter is present. In these cases an indwelling catheter is frequently used because of the temporary bladder dysfunction. The cystometrogram indicated the return of normal data and with it normal bladder function permitting the removal of the indwelling catheter. The early untimely removal of such a catheter may precipitate upper urinary infection due to back pressure with chills and fever, gravely complicating the situation, since bladder

infection is quite common in these neurologic cases with chronic bladder dysfunction (Fig. 4).

In spinal injuries usually cared for by the orthopedic surgeon the follow-up cystometric work is again of great value. It will indicate the retrogression of edema of the cord, the absorption of a blood clot, etc., by the evidence of returning normal function in a paralyzed bladder (Fig. 5).

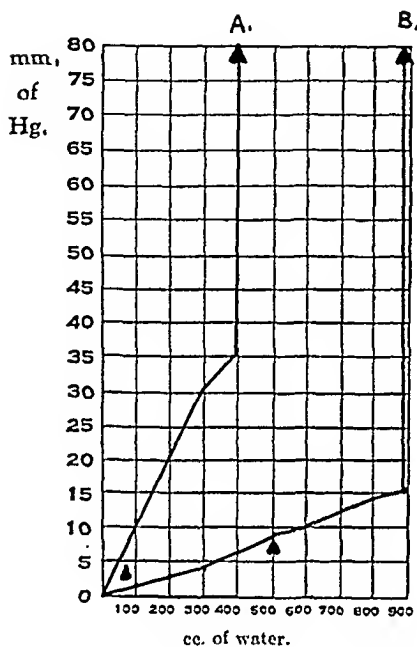


FIG. 7

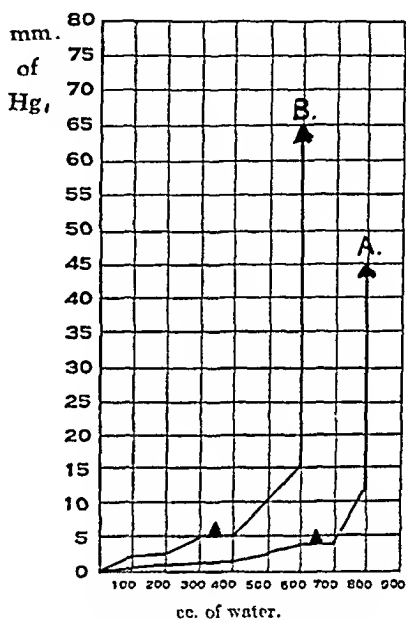


FIG. 8

FIG. 7.—Cerebrospinal lues complicated by prostatic hypertrophy. Cystometrograph A (March 22, 1935): Neurogenic bladder of hypertonic type. Cystometrograph B (July 17, 1935): Neurogenic bladder of hypotonic type. Showing the change from an irritative condition of the cord to a paralytic state in 4 months.

FIG. 8.—Contusion of spine with hematoma(?). Retention of urine for 4 days, great difficulty in urination for the following 4 weeks. Cystometrograph: A, On admission neurogenic bladder of hypotonic type; B, six months later: marked improvement but still evidence of neurogenic disturbance. No complaints, no clinical evidence of bladder disturbance. (H. H., aged 42; automobile accident.)

In medical diseases of the spinal cord, the cystometric follow-up examinations may also be very useful. Treating a case of tabes dorsalis with bladder dysfunction one can determine at intervals of treatment whether or not a therapeutic agent is bringing about improvement or whether the disease affecting the bladder is progressing in spite of the treatment (Fig. 6).

Cystometric readings may become definite criteria of the usefulness of a given therapeutic agent in cerebrospinal affections (Fig. 7).

In medicolegal work one is eager to ascertain the present status of alleged injury of the spine with bladder dysfunction. One is also

anxious to know the progress of this injury. Admitting an injury to the spinal cord resulting in temporary bladder dysfunction, one is able to clinically and graphically establish this fact, the data to be used years later to show actual injury and oppose any accusation of malingery or the reverse may be true—to actually prove malingery (Fig. 8).

The visualization of the cystometrically obtained data appears to be the most exacting, most vivid and most comprehensible way we have today in expressing disabilities of function of the urinary bladder.

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HIGHER CARBOHYDRATE DIETS IN THE TREATMENT OF DIABETES.*

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THE introduction of insulin into diabetic therapy ended a period characterized by drastic dietary restriction and made possible the closer approximation of diabetic diets to those of normal people. During the past decade there has undoubtedly been a pronounced trend in current opinion toward the use of larger amounts of carbohydrate than would have been formerly considered reasonable. Evidence in favor of such diets has been recently (1934) collected by Tolstoi,¹ who concluded that the principle appeared to be well founded. The reawakened interest in this method of treating diabetes has been due largely to the publications of Geyelin² (1926), Sansum and his collaborators³ (1926), Porges and Adlersberg⁴ (1929), Rabinowitch⁵⁻⁸ (1930-1935), and Barach^{9,10} (1930-1932).

The term "high" or "higher" carbohydrate in relation to diet is rather unfortunate, since it is neither definite nor descriptive. The content of carbohydrate in the diet is an entirely relative matter, interpretation of which is dependent upon the previous personal experience of the observer. When compared with the

* Read at meeting of the Noonday Study Club of the Wayne County Medical Society, Detroit, March 24, 1936.

normal diet, all so-called high-carbohydrate diets used in the treatment of diabetes are low, since some restriction below normal amounts is inferred by all observers. The differences in opinion regarding the fat content of the diet further confuse the issue.

In a general way the group of so-called high-carbohydrate diets may be roughly classified into the following divisions: 1, High-carbohydrate, low-fat; 2, Higher-carbohydrate, lower-fat, low-calorie; 3, Moderately-high-carbohydrate, moderately-low-fat. One might arbitrarily place the lower limit of carbohydrate in this group of diets at roughly 100 gm. per day. In some instances as much as 350 gm. have been given.

Experimentally, Watson and Wharton¹¹ have compared the effects of such diets with the results obtained from administering a low-carbohydrate, high-fat diet in 27 well-controlled cases using insulin. They reached the conclusion that increasing the carbohydrate led to an increasing tolerance, provided the fat was kept below 100 gm. daily. The patients' preference was for a moderately high-carbohydrate diet with a moderately low amount of fat. They observed that the patients felt better when larger amounts of carbohydrate were provided. The most important criticism of this work is that patients were not kept for sufficiently long periods on each type of diet.

Rabinowitch⁸ has recently reported his experience over a 5-year period when using the high-carbohydrate, low-fat, low-calorie diet in comparison with 5 years' use of the high-fat diet. He found a remarkable diminution in the amount of insulin required when using the new diet. An average dose of only 10.6 units of insulin per day was necessary, in contrast to 31.8 units using the older type of diet. Many more patients were able to do without insulin entirely and the average blood cholesterol value was much lower.

Geyelin¹² (1935) reported 150 cases treated over a 10-year period and observed that the effectiveness of each unit of insulin per gram of carbohydrate increased with carbohydrate elevation and lowering of the fat. He used diets of comparatively normal caloric value, utilizing a carbohydrate-to-fat ratio of 3 or 4 to 1. After 10 years on this diet the patient's diabetes showed no retrogression.

Sansum and Gray¹³ have reported 7 years' use of their diet in 1005 cases, showing an average gain in tolerance. Their average diet was carbohydrate, 184 gm.; protein, 66 gm.; and fat, 82 gm., a total of 1738 calories.

The favorable effect of carbohydrate upon the glucose tolerance has been noted by many observers. Greenwald, Gross, and Samet¹⁴ (1924-1925) found a distinct lowering of glucose tolerance produced by experimentally feeding carbohydrate-free diets and the effect appeared to be greater if fat was increased. Joslin¹⁵ has noted clinically that diabetics live longer, even in the presence of glycosuria, if the carbohydrate is not too low. He further states,¹⁶ "A carbo-

hydrate tolerance, unutilized, retrogrades." The action of the repeated ingestion of glucose upon the blood sugar of a normal man, the Staub-Traugott effect, is well known and was confirmed on both normal men and diabetics by Hamman and Hirschman¹⁷ in 1919. The phenomenon partially accounts for the fact that larger doses of insulin may be used before breakfast than at other periods throughout the day.

In the light of these observations the recent contributions of Himsworth^{18,19} are particularly interesting. Using normal men, a depressed tolerance curve resulted following fat feeding and an increased tolerance was observed following carbohydrate diets. Various diets were devised in order to determine the factor involved, which was proven to be the absolute amount of carbohydrate present in the diet. This factor likewise is responsible for increasing sensitivity to insulin. Based upon the percentage change in tolerance, utilizing diets containing from 50 to 425 gm. of carbohydrate, he plotted curves showing the general relationship between glucose tolerance and carbohydrate. If the carbohydrate fell below 100 gm., tolerance more rapidly declined, until a comparatively slight decrease below 50 gm. resulted in a proportionately greater reduction in tolerance, which suggests a possible explanation for some cases of diabetes exhibiting a sudden onset of symptoms.

With Marshall²⁰ he then analyzed the diets of 143 cases of diabetes in comparison with two comparable series of normal people and by both quantitative and qualitative methods established that the majority of diabetics, before the onset of their disease, preferred diets containing excessive amounts of fat. Insulin sensitivity of these patients, when computed according to his previously prepared charts, showed that the group as a whole, prior to the development of their diabetes, exhibited a 20% lower insulin sensitivity than that of normal people.

Himsworth²¹ recently compiled the available data on dietary habits throughout the world, which, upon correlation with available mortality tables, show a definite curve of relationship. The groups utilizing the greater-carbohydrate and lower-fat diets have the least diabetes and *vice versa*. He has recently commented²² that probably two types of diabetes occur: Insulin-sensitive cases, due primarily to insulin deficiency, and another group of insulin-insensitive patients. The reaction of each to carbohydrate is probably different.

Method. We began the use of higher-carbohydrate diets at the Grace Hospital in 1929 and within about 6 months had transferred practically all the patients to the new diet. Our method consisted in the main of beginning with a basic diet of approximately carbohydrate, 100 gm.; protein, 60 gm., and fat, 50 to 60 gm., with increasing amounts of carbohydrate added as improvement became evident. Never less than 100 gm. of carbohydrate was given daily and if this became impossible through illness, the patient received 100 gm. of dextrose by vein every 24 hours, usually 25 gm. every 6 hours. The Ladder method of increasing carbohydrate was utilized follow-

ing a brief desugaring period on the first diet and in general the carbohydrate of the diet *only* was increased, until an approximate level of 200 gm. had been reached. Approximately 25% of carbohydrate was given for breakfast, 35% at lunch, and 40% for dinner, in order to take advantage of the Staub-Traugott effect already noted.

By this method patients were not fed according to their basic caloric requirements as computed from standard tables. The weight, general condition of the patient, blood sugar, cholesterol, glycosuria, and sense of wellbeing were depended upon for control. Considerable variation in diet was necessary in order to satisfy individual cases and circumstances and the effort was made to treat the patients individually, making their diets as comfortable as possible. In a few instances it was later necessary to increase the fat content of the diet beyond 100 gm. in order to maintain weight, but these cases were exceptional.

Throughout the period we made no effort to spare insulin. The criterion for the use of insulin was arbitrarily whether or not the patient became sugar-free within a week or two on the diet (carbohydrate, 100; protein, 60; fat, 60) originally prescribed. Since there is considerable difference in coöperation between private and clinic patients, due to economic factors, we have utilized only the clinic group for purposes of comparison and have chosen to take averages from the two groups over 5-year periods. These results* are shown in Tables 1 and 2.

TABLE 1.—GRACE HOSPITAL DIABETIC OUT-PATIENT DEPARTMENT. AVERAGES.

	1925-1929 (Group I)	1930-1934 (Group II)
Cases	204	431
Average diet	C 75-P 62-F 117 = 1601 cal.	C 181-P 69-F 74 = 1666 cal.
Blood sugar (fasting) on admission (average) mg./100 cc.	229	219
Blood sugar (fasting) during observation, mg./100 cc.	192	176
Insulin patients (per cent)	31	53
Insulin daily average units	29.4*	23†
Glucose value of diet	122	228
Insulin-glucose ratio	1:4	1:9
Average weight loss during observation, lbs.	4	1
	* 64 patients.	† 229 patients.

TABLE 2.—GRACE HOSPITAL DIABETIC OUT-PATIENT DEPARTMENT. MORTALITY.

	1925-1929		1930-1934	
	Cases.	Per cent.	Cases.	Per cent.
Postoperative	5	2.4	3	0.7
Coma	8	3.9	1	0.2
Acute infections	4	1.9	6	1.4
Tuberculosis	5	2.4	3	0.7
Arteriosclerosis	11	5.4	8	1.8
Untraced	5	2.4	2	0.5
Total	38	18.4	23	5.3

* I wish to acknowledge my indebtedness to Dr. Daniel B. Marcus, clinical assistant, and Miss Meriel Colwell, dietician, whose detailed study of each individual chart made this analysis possible.

Discussion. We have had a strong impression since beginning the use of this diet that the patients have been decidedly easier to manage than they were under the lower carbohydrate regimen. Upon analysis of the actual statistics, a few points are rather striking. In spite of having a considerable number of patients taking from 250 to 350 gm. of carbohydrate daily, the average carbohydrate intake is only 180 gm. and the total daily caloric values of the two diets are roughly comparable (1600-1700 calories daily). Nevertheless, the average weight loss over the 2 5-year periods was only 4 pounds and 1 pound, respectively. The average fasting blood sugar of 176 found with Group II is somewhat better than that of Group I. We have presented no data on cholesterol values, having had no comparable experience with the early group, but have found them quite easy to keep within normal bounds.

The experience with insulin is particularly interesting. Following an arbitrary standard for its use, we have increased the proportion of insulin to non-insulin users from 31% in Group I to 53% in Group II. At the same time an average of 6.4 units less insulin per day per patient has been necessary in the high-carbohydrate group. When compared with the total glucose value of the diets, more than twice the insulin efficiency is shown in Group II (glucose value, 228) than in Group I, having less carbohydrate (glucose value, 122), which bears out the contention of Himsworth.

The mortality statistics were rather surprising. Undoubtedly, not all factors operative here can be attributed solely to diet. Due credit should be given to increasing experience in the use of insulin and particularly to the readiness with which we now utilize it. What was formerly a "last shot in the locker" now has become our "range finder." Nothing is lost by the early use of insulin. It is noteworthy that postoperative deaths were infrequent in the latter series, although at least five times as many operations were performed.

Safety for a diabetic depends upon his having a liver full of glycogen, instead of a liver infiltrated with fat, and this can readily be obtained in most instances by the use of insulin with adequate carbohydrate feedings, or by glucose and insulin, parenterally if necessary.

Conclusions. 1. Evidence in favor of carbohydrate diets in diabetes seems well established, both clinically and experimentally.

2. A comparison between two series of patients has been presented. In Group I a moderately-low-carbohydrate, moderately-high-fat diet was used, while in Group II a moderately-high-carbohydrate, moderately-low-fat diet was administered.

3. The patients in Group II stated that they felt better; the diet was found to be more comfortable; it was cheaper; and an apparent increase in the efficiency of insulin resulted.

4. Coma mortality was practically abolished and the other complications were more easily managed.

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A NOTE ON GLUCOSE TOLERANCE IN PAGET'S DISEASE (OSTEITIS DEFORMANS).

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SOME years ago we happened to find in 2 cases of Paget's disease of bone (osteitis deformans) glucose tolerance test curves which were marked by a rapid rise to a high level, followed by an equally

rapid descent. Since then we have collected 6 more cases. The results of the glucose tolerance test in these 8 cases are here presented.

The method employed was that of MacLean¹ using capillary blood obtained by a finger prick. Fifty gm. of glucose were taken by mouth, and determinations of blood sugar made before, and at half-hour intervals after taking glucose. Unfortunately circumstances prevented the collection of urine during the test period in 4 cases.

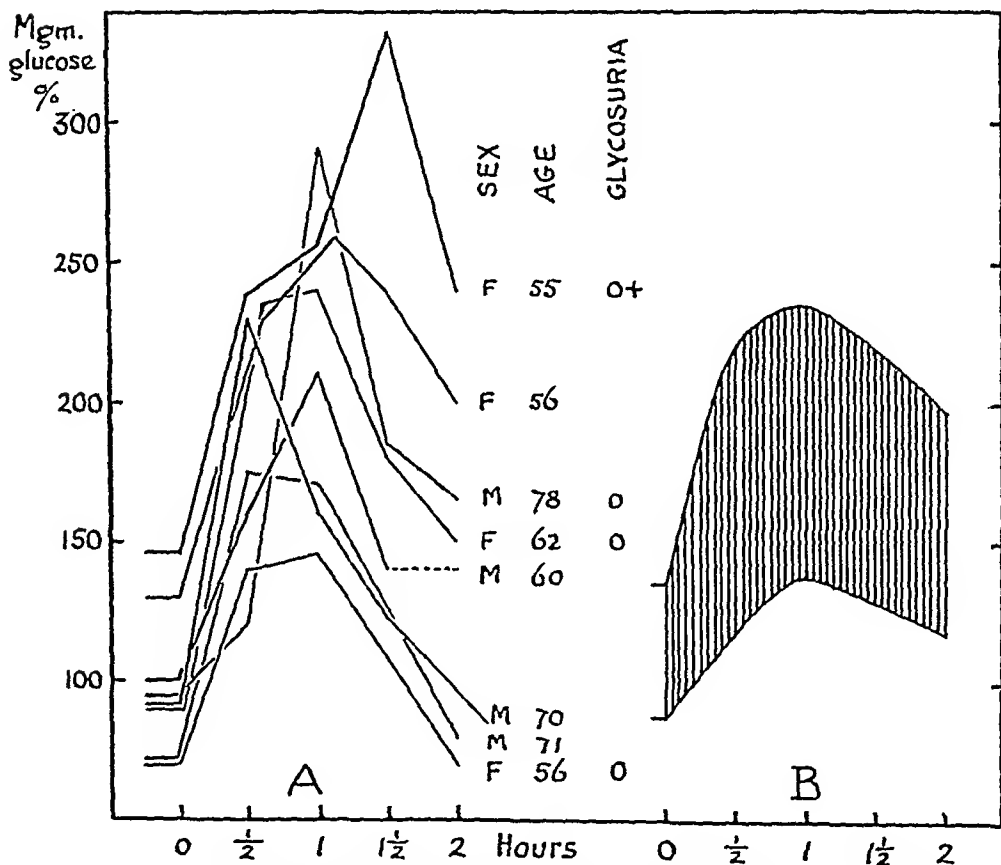


FIG. 1.—Glucose tolerance test in 8 cases of Paget's disease of bone (A compared) with the normal for people of similar age (B).

In the accompanying figure are shown:

(A) the curve from these 8 patients, together with sex, age and presence or absence of glycosuria during the test. The ages varied from 55 to 78.

(B) a shaded area, into which fall, according to Faber and Hansen² the blood-sugar curves (capillary blood) of normal individuals between the ages of 60 and 75. This area is shown for comparison with the curves in (A).

It will be seen that in all instances but one the fasting blood-sugar

level is within normal limits, but that in the first half hour 4 of these 8 curves exceed the normal limits, 4 in the second half hour, and 2 in the third half hour. All curves dropped rapidly by 2 hours, and although only 3 returned to the normal blood-fasting level, all but one returned to within the limits of normal men of the age 60 to 75. In brief about half of these curves are marked by a rapid rise and a rapid fall. The remainder fall within the limits normal for that age.

Discussion. The amount of glucose absorbed by the intestine, and therefore the peak of the blood-glucose curve, rises with the dose of glucose administered up to a maximum of 30 to 50 gm. (Hansen³). Larger doses have no effect on the curve, since, as shown by Cori,⁴ absorption from the intestine cannot surpass this maximum rate. Since we administered the standard dose of glucose, 50 gm., the high peak in our cases has some other origin. It has been further shown that the mechanism for the utilization of glucose "is accelerated as the blood sugar rises higher until, at the peak of the curve, utilization rate overtakes, and then surpasses the absorption rate, in spite of the fact that the absorption may still remain at its maximum" (Peters and Van Slyke⁵). It would appear then that in half of our cases something is causing a delay in the outset of utilization, but that the latter, once started is, in most cases, fully as rapid as in normal people. This would appear to eliminate any insulin fault. Of the remaining causes of hyperglycemia, namely, disordered function of thyroid, adrenals and pituitary, clinical examination failed to incriminate the first two, while according to a recent review (Evans⁷) the sugar curve with rapid rise and fall seems to indicate hyperpituitarism. Whether this is true or not remains to be proved. It is however of interest to recall that the bony changes in the thickening skull of Paget's disease result in pressure on, and diminished function in various cranial curves, e. g., optic, auditory, and other nerves. It seems reasonable to suppose that in some cases similar pressures are found around the pituitary fossa with alteration in pituitary function. That such bony changes do produce hyperglycemia of the type recorded in some cases of acromegaly has been known for many years (Loeb, 1883;⁸ Maric, 1889⁹).

More recently Colwell,¹⁰ in a review of the literature, showed that about 40% of acromegalias and about 10% of other pituitary diseases (tumor, cyst, tubercle, syphilis, etc.) have glycosuria. According to Peters and Van Slyke,⁶ in the earlier (hyperpituitary) stage of such diseases the glucose intolerance varies from a slightly increased alimentary hyperglycemic response (such as is seen in our cases) to a glycosuria indistinguishable from mild or severe diabetes, and further, that the fasting blood-sugar level is often within normal limits. Our curves are therefore compatible with hyperpituitarism. Unfortunately no Roentgen ray examinations of the skull were made in our cases, nor have we been able to find any

literature recording changes in the pituitary fossa. We are therefore presenting these observations in the hope that other investigators of this disease might be able to throw further light on these obscure alterations in sugar metabolism.

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A CASE OF AGRANULOCYTOSIS FOLLOWING INGESTION OF CINCHOPHEN.

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A PATIENT who had been taking cinchophen daily for 3 weeks was recently admitted to this hospital suffering with an illness which proved to be agranulocytosis. After investigating all of the possible causes we became convinced that this drug contained the leukotoxic agent which was responsible for the granulocytopenia. As cinchophen is prescribed freely and because of the serious nature of agranulocytosis we felt that our observation should be reported.

We could find no case reports in the literature of agranulocytosis caused by cinchophen.* Schittenhelm¹ recently remarked that cinchophen was capable of producing this condition but unfortunately published no reports of illustrative cases.

Cinchophen (and the same is true of amidopyrin) has been admin-

* In Fitz-Hugh and Comroe's article in this journal (185, 552, 1933), orthoiodoxybenzoate (which contains cinchophen) is incriminated as the cause of agranulocytosis in one of their cases.—EDITOR.

istered in varying dosages to countless numbers of patients without untoward effects. In those relatively rare instances in which ingestion of the drug is followed by severe intoxication giving rise to acute yellow atrophy of the liver, or as in this case granulocytopenia, it appears logical to assume that some alteration within the body induced a degree of susceptibility that does not ordinarily obtain.

Case Report. W. F., a white male, bartender, aged 34, was admitted to the hospital on April 27, 1935, complaining of vomiting, fever, marked weakness, and polyarticular pain and swelling of 2 days' duration.

Pertinent findings in his history were 4 attacks of gonorrheal urethritis over a period of 14 years. Associated with the last 3 of these was a polyarthritis which kept the patient bedridden for periods of 8 to 10 weeks in each instance. The last of these episodes which occurred following specific exposure 5 months prior to his entering the hospital has continued with remissions to the present time.

One month preceding the onset of the acute illness for which he was admitted to the ward, the patient was treated in the dispensary of this hospital for urethral strictures and joint pains. He received local treatments for the urinary difficulty and 7 intramuscular injections of Lactigen. Lactigen is not known to have any depressing effects on the bone marrow. These were followed by no noteworthy alteration in the severity of the arthritic symptoms nor was any indication of a general reaction observed. Commencing 3 weeks immediately preceding admission, the patient was given cinchophen— $7\frac{1}{2}$ grains 3 times daily. He took this medication regularly, as ordered, until 2 days before he entered the hospital when he became suddenly ill with the symptoms described above.

On admission he was acutely ill; his temperature was 104.8° F, the pulse rate was 120 and the respirations 24 per minute. There were a few palpable cervical lymph nodes. These were not tender. The lungs were clear and resonant throughout. The cardiac apex was felt in the fifth interspace, 11 cm. from the midline. The heart sounds were distant, the rhythm was regular, and no murmurs were heard. The liver was palpable two fingers' breadth below the right costal margin. The prostate was soft and moderately tender. The external genitalia appeared normal.

Marked tenderness was elicited over all dorsal and lumbar vertebrae and both sacroiliac joints. There was an effusion in both knees. Both ankles and tarsal joints were tender and hot. There was no dyspnea, no jaundice, no petechiae. The mouth and nasopharynx were normal in appearance. The spleen was not palpable. There was no generalized lymphadenopathy.

Blood count on the fourth day of the illness revealed: Hemoglobin, 68%; R. B. C., 3,680,000; W. B. C., 7,000; neutrophils, 1%; non-segmented, 2%; eosinophils, 2%; monocytes, 1%; myelocytes, 1%.

The blood sedimentation rate was 66 mm. in 45 minutes.

These findings suggested the diagnosis of agranulocytosis, as against such possibilities as gonorrheal arthritis, endocarditis of rheumatic or gonorrheal origin, or septicemia.

A second blood count on the sixth day of the illness showed a total white blood cell count of 1800, 92% of which were lymphocytes, 2% non-segmented neutrophils, 2% eosinophils, and 4% myelocytes. The platelets numbered 128,000 per c.mm.

Blood chemical studies, including icteric index were within normal limits on two occasions. Wassermann and Kahn tests, and G-C fixation of the blood serum were all negative. The same procedures were repeated on

fluid aspirated from the left knee joint and these too were negative. Smears of the fluid showed numerous neutrophils but no bacteria. The culture was sterile.

Two blood cultures showed no growth each after 5 days' incubation. Prostatic smear revealed numerous Gram-negative extracellular diplococci. Urinalysis disclosed a faint trace of albumin and a few white blood cells. Urine examinations for arsenic, bilirubin, and urobilinogen were negative. Stool cultures revealed *Staph. albus* and *Strep. anhaemolyticus*.

The patient grew progressively worse during the first week of the illness. Ulcerations of the gum, lip, palate, pharynx and anus were noted. Abdominal distention and mental confusion appeared, and the hyperpyrexia continued. Concurrently the white blood cell count diminished to 1,000 per c.mm. The ulcerations showed necrosis with no reaction in the surrounding tissues, apparently due to the absence of neutrophils.

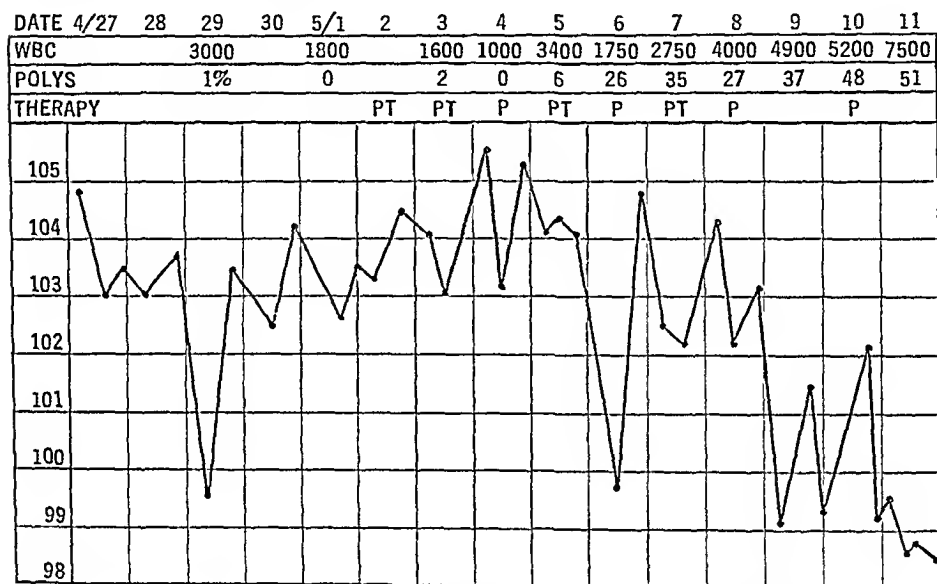


CHART I.—Temperature curve and leukocyte counts. P = Pentnucleotide injection. T = blood transfusion.

Pentnucleotide therapy was instituted on the 8th day of the illness (the 6th hospital day) and some improvement in the total white cell count was noted 2 days later. Because of the critical condition of the patient, it was deemed necessary to administer blood transfusions also. Four were given, about 400 cc. of blood being injected each time. In addition, Pitressin served effectively in combating the abdominal distention.

Improvement in the blood picture preceded clinical improvement by several days and recovery was marked by gradual healing of the local lesions as the temperature fell by lysis. The white blood cell count rose to 8300 with 50% neutrophils prior to discharge (Chart I).

It is interesting to note that the polyarthritides abated after the first few days of the illness as the fever reached its highest level. The patient remained entirely relieved of this symptom at the time he left the hospital.

Since discharge, 6 months ago, the patient has experienced mild migratory joint pains and recurrence of the urethral discharge. Otherwise he has been symptom-free except for some weakness. The white blood cell count has varied between 7800 and 11,600 and the neutrophils between 36% and 59%.

Sternal puncture on the 12th day of the illness revealed a hyperplasia of the bone marrow with predominance of the younger granular elements. This, according to Fitz-Hugh and Krumbhaar,² Reich³ and others, is characteristic of at least one variety of agranulocytosis and appears to be due to a maturation arrest. Symptomatic agranulocytosis has been observed principally following the use of the arsenicals, gold salts, and drugs containing the benzene ring.

Discussion. In reviewing this case, we have not been unmindful of the possibility of a mere coincidental relationship between the ingestion of cinchophen and the development of granulocytopenia. Indeed the identical question arose when amidopyrin was first recognized as a possible etiologic factor in this entity. However, investigation of the numerous cases as they appeared revealed certain features which invariably became evident following shortly upon the administration of the toxic agent.⁴ There was acute onset with progressive severe neutropenia but without concomitant reduction in hemoglobin, erythrocytes or platelets. There was also development of distinctive local lesions and characteristic bone marrow picture. The spleen was not detectably enlarged nor were hemorrhages present in any of these cases. The course was rapid terminating in recovery or death.

All of these features were present in the case herein reported. The onset was acute and followed immediately upon the ingestion of cinchophen. With the development of prostration there was almost total disappearance of granulocytes from the peripheral blood stream (relative lymphocytosis as high as 98%) while the erythrocyte, hemoglobin and platelet determinations varied only slightly from the normal. There were no hemorrhages, splenomegaly or generalized lymphadenopathy. Ulcerations appeared in the mouth and throat and about the anus. The sternal puncture revealed a picture of "maturation arrest"² which is accepted as diagnostic at least in one form of agranulocytosis.

There remains the question whether cinchophen contains in its structural constitution a substance which when yielded within the body is capable of exerting a leukotoxic effect. Cinchophen is phenylquinolin carboxylic acid⁵ and under certain conditions may liberate free benzene⁶ or nitrophenols.⁷ Compounds containing either of these are known to induce toxic degeneration of the liver⁸ or a paralyzing effect upon leukopoiesis as in arspenamin, amidopyrin, and dinitrophenol poisoning.⁹

Experimentally it has been possible to detect the specific leukotoxic action of this group of chemicals. Climenko¹⁰ has demonstrated in rabbits that following the administration of amidopyrin or dinitrophenol, and so on, the leukopoietic system fails to give normal response to parenteral injections of nucleic acid, namely, a transient leukocytosis; and, in fact, that this ability is lost long before any change can be observed in the cellular constituents of the

peripheral circulation. In other words, the action is directly on the bone marrow which manifests a marked hyperplasia similar to that seen clinically in agranulocytosis.

In our patient there was present no other condition such as aleukemic leukemia, Hodgkin's disease or metastatic bone carcinoma, in the course of which severe neutropenia may occur.

Summary. A case is reported where agranulocytosis occurred during the administration of cinchophen and subsided after its withdrawal. Suggestions concerning the mode of action and a possible contributory factor responsible for the patient's susceptibility are offered.

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BOOK REVIEWS AND NOTICES.

THE FOOT. By NORMAN C. LAKE, M.D., M.S., D.Sc. (LOND.), F.R.C.S. (ENG.), Senior Surgeon and Lecturer on Surgery, Charing Cross Hospital; Surgeon, Bolingbroke Hospital, etc. Pp. 330, 95 illustrations. Baltimore: William Wood & Co., 1935. Price, \$4.50.

THIS is the most comprehensive work to date on foot troubles. It recounts every condition from hyperidrosis to thromboangiitis obliterans. The chapter on examination of the feet is a postgraduate lesson for practitioner and specialist. Even such sections as evolution, embryology and anatomy may be read without boredom. Interest can be found in the sections on mechanics of gait and history of shoes. Then it assumes the conciseness of a manual. The discussion of fractures and dislocations is much too condensed to be of reference value. The treatment of the many foot complications mentioned in its text is too general and too brief to be informative. The Reviewer, however, closes the book, feeling it to be a valuable addition to any library in spite of its abridgement, and hopes that the author and publisher will bring out a more detailed and fully illustrated second edition.

J. N.

TUBERCULOSIS, Vol. 16 of Clio Medica Series. By GERALD B. WEBB, former President, National Tuberculosis Association; Lecturer on Medical History, University of Colorado; President, Colorado Foundation for Research in Tuberculosis. Pp. 205; 17 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, \$2.00.

THIS monograph is another of the valuable historical series "Clio Medica," and carries a foreword by the editor of the series, Dr. E. B. Krumblhaar. In it the author has succeeded in presenting a comprehensive story of the development of our knowledge of tuberculosis in brief form, without sacrificing literary quality. Although few important events are left out, space has been saved by precision of statement and stress only of the most significant. Lengthy arguments over priority are omitted, for, as noted in a quotation from Frances Darwin, "In science credit goes to the man who convinces the world, not to the man to whom the idea first occurs." Due notice is taken, however, of some who were merely unfortunate in lack of recognition in their own time, such as William Stark, who actually anticipated Laennec in much credited to the latter.

It is interesting to those concerned with the modern attack on tuberculosis that the opening chapter is on epidemiology and the final one on legislative prophylaxis. The early public health measures of Hermann Biggs, well known to specialists in tuberculosis, but not so well known to the medical profession in general, are credited with their deserved importance. The story beginning in ancient times is carried up to the present, with indication of modern trends of research.

Treatment accorded to climate, so often a subject of partisanship, is temperate, and the modern enthusiasm for more active measures has not prevented a sound emphasis on the value of the older, conservative treatment by rest alone. The book is heartily recommended to those who wish to learn the significant events in the history of the disease quickly.

E. L.

THE COMMON COLD AND INFLUENZA. Their relationship to other infections in man and animals. The Nature of Disease Annual Reports for the Years 1934 and 1935. By J. E. R. McDONAGH, F.R.C.S. Pp. 152. London: William Heinemann, Ltd., 1936. Price, 12s. 6d.

LET the Reviewer say at once that this volume throws more light upon the nature of the author than upon the nature of disease. The book consists of a philosophic discussion of disease based upon the author's theory "that there is only one disease and one cause in man and animals alike" (p. 119). The cause is the activity of short waves emanating from space (cosmic rays) and from bacteria. Pathogenic bacteria are all mutations of *B. coli communis*, illustrated by a chart showing six ladders proceeding away from the parent form. Disease is due to the hydration of protein particles after their dehydration under the influence of short waves. Bacteria of the intestinal canal are the offenders and they undergo cycles of activity. By quoting percentages of various bacteria found in two intestinal canals of animals and man, the author shows to his satisfaction their relationship to disease. He gives no figures from which the percentages are computed. He describes no technique which was used. He quotes no references to work done by others.

For prevention and treatment for the common cold and influenza he recommends high colonic irrigation, ultrashort wave therapy and oral or subcutaneous doses of washings made from emulsions of the patient's intestinal organisms ("Anepidem"). This treatment, with minor modifications, was found to be successful in quoted cases of lobar pneumonia, cerebral edema, rheumatoid arthritis, sciatica colitis, mucous colitis, asthenia and myasthenia, thrombophlebitis migrans and eczema.

The author is unimpressed by the work of Smith, Andrewes, and Laidlaw, in London, and Francis and Shoppe, in the United States, whose work he describes without mentioning their names or giving references to their papers.

The whole book is unscientifically presented, is tiresomely repetitious and unworthy of consideration.

H. P.

DIE TUBERKELBAZILLÄMIE IN IHRER AUSWIRKUNG AUF DIE GESAMTMEDIZIN.

By PROF. DR. ERNST LOEWENSTEIN, Vienna, mit einem klinischen Teil von PROF. DR. CARL REITTER, PROF. DR. WILHELM NEUMANN und PROF. DR. OTTO KREN. Pp. 388; 4 plates, 2 of them colored. Leipzig: Franz Deuticke, 1936. Price, Paper, M.20; Bound, M.23.

This book represents the picture of tuberculosis gained by the author after 35 years of laboratory research on its pathogenesis. The views of Loewenstein, some of which are revolutionary, are now well known throughout the world. They have elicited confirmatory evidence in widely separated quarters and much controversy. This is not the place to discuss the merits of the opposing views. Loewenstein's book serves the useful purpose of bringing together between two covers statements of his theories on each of the varied pathologic states in which he feels the virus of tuberculosis is concerned, theories built on evidence previously widely scattered in the current medical journals. In analyzing his picture it is perhaps in order that, distinctive and individualistic as it is, it represents but one phase of the still larger revolt against the conventional bacteriology of tuberculosis. The granular forms, the ultravirus and the dissociated forms, have filled the literature in recent years. Loewenstein, using a medium and culture method of now universally recognized value, has perhaps departed the furthest from the conventional field. According to his view the typical anatomic tuberculous structure represents but a short facultative phase in the cycle of tuberculosis, a disease, in his opinion, characterized by a

whole series of non-nodular ailments, having in common only their origin through the tubercle bacillus, and more specifically a tubercle *Bacillus* bacillema. His studies have brought him to include in his picture wide variability in the form of the virus of tuberculosis, not uncommon fetal transmission, frequent alimentary origin, bacillema in all forms of the disease, and a tubercle *Bacillus* bacillema in such dissimilar diseases as pulmonary tuberculosis, rheumatoid arthritis and dementia præcox. The present volume, well printed and in handy size, affords easy opportunity for examining in detail the evidence back of these views. E. L.

THE SURGICAL CLINICS OF NORTH AMERICA. VOL. 16, No. 1 (CHICAGO NUMBER—FEBRUARY, 1936). Pp. 356; 78 illustrations. Philadelphia: W. B. Saunders Company, 1936. Price, Paper, \$12.00; Cloth, \$16.00 (per clinic year, February–December, 1936).

THIS, the first number of the 1936 series, inaugurates a new kind of clinical presentation. To quote from the publishers: "In this, and in future Numbers, we shall present a Symposium on some surgical subject of universal interest. The Symposium in the February Number on Cancer of the Cervix, will show how the practical phases of the subjects are presented. The purpose of these Symposia is to give the practicing surgeon the benefit of the actual clinical experience of recognized authorities in the diagnosis and detailed management of his own cases—disease as it is encountered in daily bedside practice.

"The balance of each Number will present approximately fifteen clinics on almost every phase of surgery—the head, neck, thorax, abdomen, the genito-urinary tract, obstetrics, gynecology, the extremities, etc. And here again, we shall present the management of run-of-practice surgical conditions. The recitation of long case histories, the inclusion of rare surgical conditions and the too highly scientific and abstract problems of surgery will find no place in these new Surgical Clinics." In the present number, for instance, there is a 58-page article on Manipulative Surgery by Dr. Philip Lewin, while Appendicitis (Bevan), Sprains (Jennings), Fracture of the Jaw (Moorhead), Spastic Paralysis (Chandler), Breast Cancer (Malcolm) and Gangrene (de Takats) receive extended treatment.

E. K.

THE THYROID, SURGERY, SYNDROMES, TREATMENT. By E. P. SLOAN, M.D. Edited by Members of the Sloan Clinic, GUY A. SLOAN, M.D.; H. P. SLOAN, M.D.; FRANK DENEEN, M.D.; H. W. WELLMERLING, M.D., and O. H. BALL, M.D. With a foreword by WILLIAM SEAMAN BAINBRIDGE, M.D. Pp. 475; 99 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, \$10.00.

DR. SLOAN states in the preface to this very interesting and instructive monograph that, "the aim of this book is to recount the working theories and conclusions of a surgeon who has devoted 25 years of his life exclusively to goiter work." The work is not intended to be encyclopedic. There are 20 chapters, 16 of which are directly concerned with the thyroid gland; 1 on parathyroids, and 1 on thymus. One chapter consists of a short historic survey and the final one is on nomenclature and classification. There is a good working bibliography and an excellent index of subjects and names. The chapter on General Anatomy and Physiology, while interesting, is much too brief for a monograph of this size. It is the weakest part of the volume and will prove disappointing to those who look to it as a reference work. The chapters on etiology, prophylaxis, pathology, symptomatology, prognosis and surgical anatomy are extremely well done. The illustrations

of the surgical anatomy of the neck, several of which are in color, are splendid. In the chapter on preoperative treatment, the medical care of the patients who also have severe cardiac disease could have been well amplified. Certain of the drugs used by the author in the thyro-cardiacs are not generally used.

It is stated that iodine is best administered in the form of Lugol's solution, but that some patients tolerate iodoform better. The evidence at present strongly indicates that the iodine in Lugol's solution is absorbed from the intestinal tract in the form of sodium iodide, a form in which it can be readily administered. The sections on operative technique and postoperative management are full of the author's ideas gained from an extensive experience in thyroid surgery.

The criticisms which have been enumerated are more than offset by the wealth of material which the author and his associates have placed in this monograph. It is much more than a surgical treatise. It should be a real value to a large group of practitioners whether they be in private practice or public health work. The publisher should be commended for the paper, the type and the format, which are excellent.

I. R.

THE CHEMISTRY OF NATURAL PRODUCTS RELATED TO PHENANTHRENE.

By L. F. FIESER, Associate Professor of Chemistry, Harvard University. A monograph of the American Chemical Society series of scientific and technologic monographs. Pp. 358. New York. Reinhold Publishing Co., 1936. Price, \$6.50.

The publication of this monograph is very timely. Since the original clarification in 1932 by Rosenheim and King of the structure of bile acids, there has been a great increase of knowledge concerning the structure and physiologic properties of a host of chemical substances of the class of sterols related to either cholesterol or coprosterol. It appears that Nature is exceedingly partial to certain chemical configurations and reverts to them time and time again in her quest for "functional" agents. Thus, bile acids, cholesterol, vitamin D, the female and male sex hormones, embryonic "cell organizers" and cardiac stimulators all have in common the skeleton structure, phenanthrene cyclopentane. Add to these substances certain carcinogenic compounds which are related chemically to the above, and it is easy to realize the prime importance to medicine of this line of chemical development.

Fieser, himself engaged in research upon "carcinogenic sterols," treats the whole subject with admirable clarity and evident enthusiasm. The material is so well organized that a non-chemist can find large profit in even the purely chemical sections. The volume is not only a reference work, but an exceedingly readable fundamental text. It is whole-heartedly recommended to all readers.

D. D.

STRENGTH OUT OF SUFFERING. A translation of "Servitude et Grandeur de la Maladie." By FRANCE PASTORELLI. Pp. 224. Boston: Houghton Mifflin Company, 1936. Price, \$1.50.

This autobiographic book has also appeared in France and England, each time under a different title. For 15 years an invalid, the last 4 spent in bed, this sufferer from incurable heart disease tells us that from the first, a famous professor gave her but one more year of life. Frustrated in her effort to be a pianist—and her talent was very decided—she evolved a philosophy of sorrow, sought and found solace therein. What the Madame does not tell, though her "case history" reveals, is, that she likewise has a

psychoneurosis. However, grateful for her adjustment, she is endeavoring to aid all hopeless sufferers. But this rather poetic and prayerful presentation, shows too little restraint and too much emotion to benefit any but the psychoneurotic in need of an emotional outlet.

N. Y.

UROLOGY IN WOMEN. A Handbook of Urinary Diseases in the Female Sex. By E. CATHERINE LEWIS, M.S. (LOND.), F.R.C.S. (ENG.), Surgeon to the Royal Free Hospital; Surgeon and Urologist to the South London Hospital for Women. Pp. 100; 31 illustrations, some in colors. Second edition. Baltimore: William Wood & Co., 1936. Price, \$2.25.

THE purpose of this small work is to present only the urologic lesions peculiar to women. The incompleteness necessitated by such a scope rather limits the usefulness of the book by making it an adjunct to larger works on surgery or urology. An interesting discussion of the rather rare lesion of endometriosis of the bladder is noted, as well as a section on vesical neck obstruction. Among the revisions are the discussion of changes of the ureters during pregnancy and menstruation, the dietary treatment of pyelitis and on nephroptosis. There is a marked tendency to recommend proprietary therapeutic agents by their trade names. The subject matter is well handled and the book should be useful, though in no sense a work of reference.

P. W.

ILLUSTRIOUS CONTRIBUTIONS TO PUBLIC HEALTH. A Souvenir. Prepared for the Dedication Exercises on Tuesday, November 26, 1935. By CHARLES FREDERICK BOLDUAN, M.D., Department of Health, City of New York. Pp. 33; illustrated. Privately printed, 1936. Price, \$1.00. (Can be obtained from the New York Academy of Medicine.)

WHEN the new public health building was planned for New York City, the New York Academy of Medicine was asked to select 29 illustrious contributors to public health whose names were to be carved on the frieze of the new building. This brochure gives a brief account of the distinctive contributions of each, 11 Americans, 7 English, 3 German and so on from Moses to Biggs. With a paragraph or two for each, and each illustrated with a portrait, this booklet gives a pleasant approach to the history of this important subject.

E. K.

THE INTERNATIONAL MEDICAL ANNUAL. Fifty-Fourth Year, 1936. A Year Book of Treatment and Practitioner's Index. Editors: H. LETHBRIDGE TIDY, M.A., M.D. (OXON.), F.R.C.P., and A. RENDLE SHORT, M.D., B.S., B.Sc., F.R.C.S., with 36 Contributors. Pp. 555; 73 illustrations and 81 plates, some in colors. Baltimore: William Wood & Co., 1936. Price, \$6.00.

THIS volume opens with Osler's truism that a textbook of medicine must not be a yearbook. Conversely, a yearbook, which, like minutes, "must record the proceedings of the previous year," can offer information or leads to the student of medicine not to be gleaned from textbooks and only too widely scattered in current journals. Taken in this way yearbooks have their places, and when they are done as well as this one and by as distinguished a group of contributors, their value is assured. As usual, great skill has been shown in condensing a large amount of material into small space. The emphasis on treatment reflects the practical nature of the British clinic.

E. K.

MEDICAL PAPERS. Dedicated to Henry Asbury Christian, Physician and Teacher. From his present and past associates and house officers at the Peter Bent Brigham Hospital, Boston, Mass. In honor of his Sixtieth Birthday, February 17, 1936. Edited by ROBERT T. MONROE, Peter Bent Brigham Hospital, Boston. Pp. 1000; illustrated. Baltimore: The Williams & Wilkins Company, 1936.

THIS handsome volume composed of over one hundred valuable medical papers, is written by Dr. Christian's present and past Associates and House Officers. It contains not only much useful and entirely practical information for every day application in general medical practice. Even more important at a period when Medicine, in common with other professions, needs inspiring leadership, there are two articles that successfully outline a vivid word picture of the man whose wholesome influence has greatly inspired both his intimate associates and other physicians coming into intimate contact with him. In an essay entitled, "An Appreciation," by "W. T. V.," a reader who is not fortunate enough to have been one of Dr. Christian's "Boys," may learn the influences, hereditary, environmental and personal that caused Dr. Christian to become the medical leader that he is universally admitted to be. "W. T. V." states, "He (Doctor Christian) has combined within him those attributes which make him, in all probability, the greatest living trainer of men in internal medicine." The present reviewer, who possesses limited accurate information concerning medical leadership outside North America, is in perfect accord with "W. T. V.'s" statement and sincerely wishes for the sake of American Medicine that every medical school and every medical center could be equally fortunate in its sources of medical inspiration. Dr. Christian made a statement, in addressing a Fellowship of the American College of Physicians, a few years ago, that makes one pause. He said, "Physicians may be divided into two classes and two classes only: those who are learning and those who are forgetting: Those who each year know more and those who each year know less: there is no third class." The physician who reads the volume of medical papers, dedicated, very properly, to this distinguished leader of medicine at a time when he is in his productive years, will have, under pleasant and thought productive auspices, continued in the class of physicians who are a credit to their profession.

E. B.

INTERPRETATION OF LABORATORY FINDINGS. By RAYMOND H. GOODALE, M.D., Pathologist, City Hospital, Worcester, Massachusetts; Visiting Pathologist, Belmont and Fairlawn Hospitals, Worcester, etc. Pp. 170. Philadelphia: F. A. Davis Company, 1936. Price, \$2.25.

Dr. GOODALE has attempted to place into a small handbook a brief account of the more important laboratory data for the purpose of assisting a physician in an economical laboratory investigation of a disease. Obviously to incorporate the data in a small 170-page volume means the briefest possible summary. However, one may find here the answers to many questions that may confront the clinician.

Of the 4 parts, *Part One* ("Normal Values and Interpretation of Abnormal Values") is complete enough for the ordinary routine tests. The number of subjects covered is limited to those few that are well known, and those in which the technicalities are about the same in each laboratory.

In *Part Two* ("Diseases with Associated Laboratory Findings"). The useful tests are grouped according to disease, and their average findings are given. This should prove helpful to internes in formulating a plan of clinical pathologic investigation and follow-up. These data when coupled with the clinical history and physical findings should make an adequate and economical work-up for the patient.

Part Three ("The Physiologic Pathology of Body Fluids and Excreta") is brief. It is excellent in the topics covered. Much knowledge of this type should be obtained by every practitioner.

Part Four ("Preparation for Laboratory Procedures") includes the ordinary tests as outlined in Part One, and is adequate.

It is felt that if this book is consulted, there will be a marked improvement in the choice of tests, especially by internes, with a consequent lowered cost of medical care to the patient.

J. B.

ON PERCUSSION OF THE CHEST. Being a Translation of Auenbrugger's Original Treatise Entitled "*Inventum novum ex percussione thoracis humani, ut signo abstrusos interni pectoris morbos detegendi.*" [Vienna, 1861.] By JOHN FORBES, M.D. [London, 1824]. Introduction by Henry E. Sigerist, Pp. 31; 2 illustrations. Baltimore: The Johns Hopkins Press, 1936. Price, 75c.

How many physicians among the thousands daily practicing percussion know that it was discovered by Auenbrugger less than two centuries ago? How few among those that have this knowledge have read the brief 48 observations and scholia whose publication signalized the discovery? Without probing for an answer which would perhaps be humiliating, let us dwell on the pleasure and value to physician and medical student of this adequate inexpensive booklet containing John Forbes' translation, the only one ever made into English. In fact, this and Neuburger's quadrilingual reprint of 1922, the bicentennial of Auenbrugger's birth, are about the only places where an English translation can be found. The Latin original is practically unobtainable and even Corvisart's French translation (1808) a scarce treasure for the medical bibliophile. Sigerist's introduction, reprinted from the Bulletin of the Hopkins Institute, gives a useful setting to the author and his book. One wishes it could have been longer, perhaps the most successful achievement for an introduction.

E. K.

MEDICAL HISTORY OF CONTRACEPTION. By NORMAN E. HIMES, Ph.D., Medical Foreword by Robert Latou Dickinson, M.D., F.A.C.S. Pp. 521; 30 illustrations and 29 tables. Baltimore: The Williams & Wilkins Company, 1936. Price, \$7.00.

In the short time in which contraception has occupied medical and public attention to any notable extent, more than the usual amount of acrimony based on ignorance has been developed. In this field especially, then, is an impartial historic study of great practical as well as cultural value. A medico-social borderland, it has now been appropriately investigated by a sociologist whose work was scanned by a medical editorial board.

To many it will be a surprise that the practice of birth control is wide spread in primitive peoples (rather stiffly called "preliterate societies" by the author) and that the Kahun papyrus (ca. 1850 B.C.) contains contraceptive prescriptions. If Lippert's generalization is correct, "The farther a notion reaches back into primitive times for its origin, the more universal must be its extent, and its power in history is rooted in this universality," then we are dealing with a powerful force indeed. In this scholarly book the first five parts deal with Contraceptive Technique in different past ages and localities, while the last and longest part deals with the present and future. An idea of relative emphasis is furnished by the greater number of index references to Sarton or Soranus than to Margaret Sanger; and to R. L. Dickinson than to Stopes, and so on. The material collected is compre-

hensive and well documented. It is treated in such a scholastic manner that not only will the prurient be disappointed but the legitimate reader will find much of the going dry if not dusty. This is a minor fault, if fault it be, in such a subject. If the book succeeds, as it should, in impressing on its readers the past and present significance of the birth control movement, it is indeed valuable. E. K.

NEW BOOKS.

Chemical Procedures for Clinical Laboratories. By MARJORIE R. MATTICE, A.B., Sc.M., Assistant Professor of Clinical Pathology, New York Post Graduate Medical School of Columbia University; Assistant Director of the Biochemical Laboratory, New York Post Graduate Hospital; Consultant Chemist, Reconstruction Hospital, New York City. Pp. 520; 90 illustrations and 2 colored plates. Philadelphia: Lea & Febiger, 1936. Price, \$6.50.

Gynecology and Obstetrics. (Vol. XVII of *Clio Medica*.) By EDWIN M. JAMESON, M.D., Surgeon, General Hospital; Consulting Surgeon, Reception Hospital, Saranac Lake, New York. Pp. 170; 5 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, \$2.00.

Oral Hygiene and the Treatment of Parodontal Diseases. By RUSSELL W. BUNTING, D.D.Sc., Professor of Oral Histology and Pathology in the School of Dentistry of the University of Michigan, Ann Arbor. Pp. 187; 80 illustrations. Philadelphia: Lea & Febiger, 1936. Price, \$2.50.

Theory and Practice of Psychiatry. By WILLIAM S. SADLER, Chief Psychiatrist and Director, The Chicago Institute of Research and Diagnosis; Consulting Psychiatrist to Columbus Hospital, etc. Pp. 1231. St. Louis: The C. V. Mosby Company, 1936. Price, \$10.00.

Arthritis and Rheumatic Disease. By MAURICE F. LAUTMAN, M.D., Consultant to the United States Public Health Service Clinic and Director of the Department for the Study of Arthritis, Levi Memorial Hospital, Hot Springs, Arkansas. With a Foreword by MORRIS FISHBEIN, M.D. Pp. 177; 12 illustrations. New York: McGraw-Hill Book Company, Inc., 1936. Price, \$2.00.

Physician, Pastor and Patient. Problems in Pastoral Medicine. By GEORGE W. JACOBY, Past President of the American Neurological Association and the New York Neurological Society. Pp. 390; 20 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, \$3.50.

A *Diabetic Manual.* For Practitioners and Patients. By EDWARD L. BORTZ, A.B., M.D., F.A.C.P., Associate Professor of Medicine, Graduate School of Medicine, University of Pennsylvania; Chief of Medical Service B, The Lanckenau Hospital, Philadelphia, etc. With a Foreword by GEORGE MORRIS PIERSOL, B.S., M.D., F.A.C.P., Professor of Medicine, Graduate School of Medicine, University of Pennsylvania, etc. Pp. 222; 12 illustrations (2 in color). Philadelphia: F. A. Davis Company, 1936. Price, \$2.00.

Schlacke und Vitamine. Die Schlackenkost als Behandlungsweg bei Krankheitszuständen. By PROF. DR. HUGO SALOMON, Buenos Aires. Pp. 263. Wien: Franz Deuticke, 1936. Price: Paper, M. 12.; Bound, M. 14.40.

By "Schlackenkost" (roughage) the author understands food richest in cellulose, fruit acid, sugar and so on (whole-meal bread, raw fruit). On the first 100 pages he thoroughly analyzes the scientific foundation of this food. On the remaining 150 pages he discusses its application in various diseases (diarrhea, peptic ulcers, typhoid, tuberculosis, metabolic, cardiac, renal diseases and so on). W. E.

An Introduction to Psychological Medicine. By R. G. GORDON, M.D., D.Sc., F.R.C.P. (Ed.), Physician to Royal United Hospital, Bath; Physician to Bath and Wessex Orthopaedic Hospital, Bath, etc., N. G. HARRIS, M.D., B.S. (Lond.), D.P.M., Physician in Charge to Woodside Hospital; Physician for Psychological Medicine, Middlesex Hospital, etc., and J. R. REES, M.A., M.D., D.P.H. (Camb.), Medical Director, Institute of Medical Psychology. Pp. 386; illustrated. New York: Oxford University Press, 1936. Price, \$4.00.

Le Problème du Cancer. (Extrait de la Gazette Médicale de Nantes du Mois de Juin, 1936.) By DOCTEUR RAPPIN, Professeur-honoraire de l'Ecole de Médecine; Directeur de l'Institut Pasteur de Nantes. Pp. 60; 7 plates of illustrations. Nantes: Imprimerie de Bretagne, 1936. (Price not given.)

An Introduction to Materia Medica and Pharmacology. By HUGH ALISTER MCGUGAN, Ph.D., M.D., Professor of Materia Medica, Pharmacology and Therapeutics, University of Illinois, College of Medicine, Chicago, and EDITH P. BRODIE, A.B., R.N., Formerly Director, School of Nursing, Vanderbilt University, Nashville; Formerly Instructor in Materia Medica and Therapeutics, Washington University School of Nursing, St. Louis. Pp. 580; 71 illustrations and 18 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, \$2.75.

Mrs. Eddy Purloins from Hegel. Newly Discovered Source Reveals Amazing Plagiarisms in Science and Health. By WALTER M. HAUSHALTER. Pp. 126; illustrated. Boston: A. A. Beauchamp, 1936. Price, \$1.50.

Die Vererbung innerer Krankheiten. By PROF. DR. WILHELM WEITZ, Direktor der II. Medizinischen Klinik und Poliklinik an der Universität Hamburg. Pp. 197; 67 illustrations and 12 tables. Stuttgart: Ferdinand Enke, 1936. Price: Paper, Rm. 13.; Bound, Rm. 14.60.

Microbiology and Pathology for Nurses. By CHARLES F. CARTER, B.S., M.D., Director, Carter's Clinical Laboratory, Dallas, Texas; Formerly Director of Laboratories, Parkland Hospital, Dallas, and Lecturer in Bacteriology and Pathology, Parkland Hospital School of Nursing. Pp. 682; 138 illustrations and 14 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, \$3.00.

Einfluss der Gemütsbewegungen auf den Körper. (Affektphysiologie und Organneurosen.) By DR. ERICH WITTKOWER. Pp. 215; 23 illustrations and 12 tables. Leipzig: Sensen-Verlag, 1936. (No price given.)

Atlas of Congenital Cardiac Disease. By MAUDE E. ABBOTT, B.A., M.D., F.R.C.P. (CANADA), Curator of the Historical Medical Museum and Assistant Professor of Medical Research, McGill University, Montreal, Canada. Foreword by DR. PAUL D. WHITE. Pp. 72; 25 plates with more than 200 illustrations. New York: The American Heart Association, 1936. Price, \$5.50.

The Theoretical Possibility of Immunizing the Olfactory Mucosa Against Polio-myelitis Virus. By S. PESKIND, B.S., M.D., Cleveland, Ohio. Pp. 22. Cleveland: S. P. Mount Printing Company, 1936. (Price not given.)

International Clinics. Volume III, Forty-sixth Series, 1936. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, with 14 Collaborators. Pp. 339; illustrated. Philadelphia: J. B. Lippincott Company, 1936.

NEW EDITIONS.

A Text-Book of Neuro-Anatomy. By ALBERT KUNTZ, Ph.D., M.D., Professor of Micro-anatomy in St. Louis University School of Medicine. Pp. 519; 307 illustrations. Second edition, thoroughly revised. Philadelphia: Lea & Febiger, 1936. Price, \$6.00.

PROGRESS OF MEDICAL SCIENCE

THERAPEUTICS

UNDER THE CHARGE OF

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THE PRESENT STATUS OF THE CLINICAL USE OF CEVITAMIC ACID (ASCORBIC ACID) (CRYSTALLINE VITAMIN C).

THE difficulty of presenting a detailed review of the present status of knowledge concerning vitamin C becomes at once apparent when it is realized that, in the single year, 1935, approximately one thousand articles appeared throughout the world dealing with this substance and that, at present, new papers are being published at the rate of about fifty each month. The author has, therefore, elected to attempt to point out the significant trends along the lines of which profitable investigation is being engaged in and to present critical comments on present and past studies. In addition, original work based on our own research will be included where relevant.

The Chemistry of Cevitamic Acid.—The antiscorbutic properties of the citrus fruits and certain other substances have long been recognized, and numerous workers, notably Zilva,¹⁻³⁹ Hess,^{40,41} Tillmans⁴²⁻⁴⁷ and their co-workers were engaged for years in an attempt to understand and to isolate the active principle involved in this action. It remained for Szent-Györgyi⁴⁸ to isolate hexuronic acid in 1928, but its identity with crystalline vitamin C was not recognized until 1932.^{44,49-53}

This substance is an odorless, white or yellowish white crystalline powder with a melting point of from 189-192° C. The acid titration corresponds with the formula $C_6H_8O_6$.^{54,55} A summary of its physical and chemical properties with references may be found in a previous paper.⁵⁶ It was first isolated from cabbages, oranges and adrenal cortex substance and later from adrenal medulla, corpus luteum, lemon juice, paprika, green pepper, gladiolus, iris, skunk cabbage (*symplocarpus foetidus*), parsley, watercress and other sources. It has been synthesized^{57,58} as well as a number of analogues and derivatives of which some

such as *d*-arabo-ascorbic acid,^{59,63} *l*-rhamno-ascorbic acid (the enantiomorph of the fully active *l*-ascorbic acid) are inactive.⁶⁴

The Vitamin C Content of Common Foods.—The question as to whether the average diet contains sufficient vitamin C to compensate for normal utilization and loss has received careful consideration. Van Eecklen and Wolff^{64,65} have determined that a person of 70 kg. body weight needs about 50 mg. of ascorbic acid a day. Among the Dutch population the average mean intake in their studies equalled 91 mg., the lowest value being 55 mg. and the highest 124 mg. Intake is largely influenced by the consumption of citrus fruits and potatoes, although many vegetables and fruits contribute to the total. There is a considerable variation in the vitamin C content of citrus fruits and tomatoes and this is even more marked in the commercial juice products.^{66,67} (For lists of vitamin C content of foodstuffs, see Refs. 66 and 64.) It should be noted that, while breast milk usually contains sufficient vitamin C to protect against scurvy, cow's milk taken directly from the udder contains only $\frac{1}{3}$ to $\frac{1}{4}$ as much vitamin C as breast milk. Further loss in cow's milk is produced by: 1, pasteurization; 2, ageing, especially in light; 3, reheating⁶⁸ and usually 4, dilution before it reaches the infant. Hence,² there is a need for supplementary use of citrus fruit juice or other forms of vitamin C in infant feeding. The cow is known to synthesize its own vitamin C and not to depend on its content in the food. It is, therefore, unlikely that this condition can be affected significantly by changes in the cow's diet.⁶⁸ Chakraborty^{69,70} was, however, able to increase the vitamin C content of humans' milk 1.5 times by the administration of increased amounts (109 mg. daily) of vitamin C. This has been confirmed by Sellig and King.⁷¹

The Utilization of Vitamin C in the Body.—The utilization of vitamin C, taken by mouth, is not fully understood. A considerable amount is probably lost in the stool, varying amounts are excreted in the urine, and the remainder appears to be stored, utilized or resecreted as, for example, in the saliva.⁷² It has been demonstrated in various body tissues and fluids, as, for example, the adrenal,⁷³ pituitary,⁷⁴ ovary,⁷¹ possibly tumors,^{75,76} blood serum,⁷⁷ cerebral spinal fluid,^{79-81,82b} sweat,⁸¹ aqueous humor^{77,82a,83} and in the urine by many workers.

The urinary excretion of vitamin C is of importance in helping to determine the state of vitamin C nutrition of an individual. Harris and Ray⁷³ reported that the urine of normal individuals showed a rather constant daily quantity of cevitamic acid averaging 30 to 33 mg. per day. This uniformity in daily excretion of vitamin C has not, however, been found by other workers, including ourselves;^{54,85} Johnson and Zilva,⁸⁶ for example, conclude that there is no definite standard of normality as regards urinary excretion of cevitamic acid in man and cite instances in which the daily excretion reached as much as 70 to 150 mg. In our experience, the average normal excretion has been 20 to 30 mg. daily; rarely has it reached 35 mg. It has been found that further information regarding the degree of so-called "vitamin C saturation" of the body can be obtained by the use of what is known as a "test-dose method."^{73,84,86-88} The response to the test dose which should be large (500 to 1000 mg. of cevitamic acid by mouth) depends largely on the vitamin C dietary intake previous to the test. Normally,

the response in vitamin C excretion approximates 30% of the test dose within 24 hours. The peak of the excretion is reached during the second and third hours with a gradual return to the normal level towards the end of the 24 hours. A return of 20% or less represents a suboptimal state of storage. If daily large doses of cevitamic acid (100 mg. or more) are given, there will be a gradual increase up to 76 or more per cent. Schultzer found this level to be 50% in his cases.⁸⁹ This is considered to represent a state of vitamin C saturation for the individual; and continued equal dosage will not elevate the level of excretion in that person. In other words, the total ability of the individual to use or store vitamin C has been reached and the organism throws off a very high percentage of the dosage, when the sources of loss are considered. That this ability to store vitamin C is very limited is easily demonstrated by the rapidity with which the urinary excretion and blood level, to be considered later, drops on a vitamin C-free diet. As emphasized by Youmans *et al.*,⁸⁸ the state of saturation probably does not represent an optimal or normal storage of vitamin C but is an artificial state produced only by the intake of large (excessive) doses of the vitamin. The above statements apply only to the normal. As will be pointed out later, many factors may change the vitamin C metabolism and alter the urinary excretion markedly.

Sources of Error in Vitamin C Determinations.—Since methods for determining the urinary vitamin C and the test dose technique are being more generally used, a few words of warning are in order regarding the common sources of error which have invalidated some of the publications dealing with this subject. Certain other reducing substances found in normal urine, namely, glutathione, cysteine and ergothioneine, are felt by Van Eeckelin⁶⁵ to constitute a definite source of error. He also found in the urine of some diabetics another reducing substance which he felt was probably a thiosulphate. These constituents have not been generally considered to be present in sufficient quantities to change the determinations significantly, but they can be removed by precipitation with mercuric acetate before titration. The method of determination most generally employed was introduced by Tillmans^{45a} and modified in varying ways by many groups of workers. The principle involved rests on the reduction of the cevitamic acid in the unknown by titration against the dye 2 to 6 dichlorophenol-indophenol. It was soon found that the vitamin C content measurable dropped rapidly on standing, and we have studied at some length the factors producing marked error in the results.⁸⁴ The findings may be briefly summarized as follows: The dye must be carefully prepared including several washings with ether to remove a pink impurity which frequently interferes with the end-point readings. Harris and Ray⁷³ state that “. . . . The urine should be titrated immediately it is passed, or, if this is impracticable, 10% by volume of glacial acetic acid may be added as a preservative. Under such circumstances, the vitamin C in the urine may be preserved for about 10 to 12 hours with relatively little loss.” We have found, however, that the loss, under such circumstances, could be considerable. Thirteen experiments were performed in which fresh specimens of urine, acidified 10% by volume with glacial acetic acid were titrated immediately, and 2, 4, 6 and 24 hours later. Under ordinary conditions of light and room temperature, the loss, dur-

ing the stated times, averaged: 14.6%, 30.4%, 37.6% and 78.5% respectively, yet, papers have been published based on 24-hour specimens preserved as above outlined. The loss is greatly lessened by keeping the specimen in the dark or in dark brown bottles and at ice-box temperature or on ice. Acidifying the urine was definitely important, but, in our studies, sulphuric acid added until the urine reached a pH 3, as suggested by Johnson and Zilva⁸⁶ gave a greater preservative power than the acetic acid above mentioned. The use of toluene or mineral oil produces no preservative effects. If the urine must stand, the least loss, in our experience, will occur if the specimen is acidified with sulphuric acid to pH 3 and is kept in the dark at ice-box temperature. Under these conditions, the specimens showed generally no loss in the first 6 hours and varied from no loss to 12.2% loss in 24 hours.

The Vitamin C Content of the Blood.—The vitamin C content of the blood has also been studied carefully to determine its significance as an index of the state of vitamin C nutrition of the individual. There are, at present, great differences of opinion regarding the state in which cevitamic acid is present in the blood and also the value of its level as an index of the vitamin C saturation of the body. Van Eckelen and his co-workers^{79,80} have studied the amount of cevitamic acid which they claim occurs in the blood in a reversibly oxidized state. Kellie and Zilva,⁹¹ on the other hand, have presented evidence that the blood does not contain the reversibly oxidized form of the vitamin. Plant and Bulow⁸² feel that, in the blood, it is mainly present in the reversibly oxidized forms, that the reduced form is found especially in a high vitamin C diet, and that variations in the cevitamic acid in the blood affect only the reduced form. They feel that cevitamic acid cannot be oxidized in the blood either *in vivo* or *in vitro*. Mirsky, Swadesh and Soskin⁹² have modified the method of Van Eckelen in order to determine what they consider to be the total content of ascorbic acid present in the reduced form, any oxidized material being converted to the reduced form by the procedure. They state that by this method, they have been unable to determine any correlation between the total cevitamic acid content of the blood and the dietary régime. Farmer and Abt⁹³ have presented a macro and a micro method of determining the reduced ascorbic acid in the blood. They find a definite correlation between this blood level and the vitamin C intake.

The interpretation of the blood determinations by any of the suggested methods is also a matter of serious debate at present. Using the method of Farmer and Abt, we have found a normal blood level in adults to rest between 0.7 and 1.3 mg. per 100 cc. This agrees rather closely with the findings of Gabbe⁹⁴ and Farmer and Abt (in children). These figures can be made to vary considerably by a short abstinence from or intake of large doses of vitamin C. The value of a single reading is, in our opinion, questionable. We have studied the effect of the intravenous injection of a large amount of vitamin C (1000 mg.)* on the blood levels in patients with a previous poor intake of vitamin C and in those with a good vitamin C intake.⁸⁴ There are three important features to the normal response to this test: 1, an immediate rise in the blood level, which, at 15 minutes, is found to be at 4 to 10 mg. per 100 cc. of blood

* Cevitamic acid used in our studies was supplied through the kindness of Merck & Co., Rahway, N. Y.

plasma; 2, a high "normal" level at the end of 3 hours; 3, the excretion in the urine of 45% or more of the amount injected during the following 24 hours.

In a patient with a poor previous intake, the initial rise in the blood is decidedly less high and the urinary excretion is markedly lessened, both showing a tendency to storage. This test probably represents our best method for determining the vitamin C saturation state of a given individual. Similar results can be obtained by oral administration of the vitamin, but the intravenous route obviates the possibility of loss through lack of absorption.

The Fragility of the Minute Vessels of the Skin and Its Relation to Vitamin C Metabolism.—Another approach, long used to indicate the state of vitamin C nutrition of the body is the determination of the fragility of the minute vessels of the skin. In its crudest form, it was known as the tourniquet test (Rumpel-Leede phenomenon) and it has since been termed the "capillary fragility" or "capillary resistance" test, depending on the modification of the original method used. As noted above, it should more correctly be termed to include the "minute vessels of the skin," including venules and arterioles, since many of the small hemorrhages produced by whichever of the methods used are macroscopic and in the opinion of Marquardt⁹⁵ due frequently to the rupturing of the venules. Hess and Fish⁹⁶ suggested the relationship between the fragility of the minute vessels and scurvy in infants in 1914. Since then numerous workers have studied this phenomenon, using varying methods with the result that there are at least three distinct schools of thought regarding the value of this method in the determination of the vitamin C nutrition of the body: I. Those who believe that the phenomenon is useful and important and who believe that a positive pressure method is probably the most satisfactory; (a positive pressure method is one in which a blood pressure manometer cuff is applied on the upper arm, and the pressure is raised to a level sufficient to block the venous return flow) (50 mm. Hg: Gothlin⁹⁷) halfway between diastolic and systolic pressures: Wright and Lilienfeld.^{98,99} After 15 minutes the pressure is released and the petechiæ visible to the naked eye, within a definite sized area, are counted. Schultzer,⁹⁹ Stocking,¹⁰⁰ Gedda¹⁰¹ and others have had wide experience with this type of technique; II. Those who believe that the phenomenon is useful and important and who feel that a negative pressure method is more reliable and acceptable. (A negative pressure method is one in which suction of varying degrees is applied to the skin for arbitrary periods of time and either the degree of negative pressure necessary to produce rupture of the minute vessels or the number of hemorrhages produced within a given time is accepted as indication of the degree of capillary resistance.) Leading exponents of this type of technique have been Hecht,¹⁰² Wiemer,¹⁰³ Cutter and Marquardt,¹⁰⁴ Da Silva-Mello,¹⁰⁵ Dalldorf,^{106,107} Brock and Marcus¹⁰⁸ and Cutter and Johnson;¹⁰⁹ III. Those who feel that studies of the vitamin content of urine and blood, as above outlined, reveal the entire picture and that the so-called "capillary fragility tests" are misleading and of little value. Among workers who have presented evidence along this vein are Abt, Farmer and Epstein,¹¹⁰ Goettsch,¹¹¹ Anderson, Hawley and Stephens.¹¹²

For detailed reports concerning the above viewpoints and evidence presented, the reader is directed to the references given above, but certain comments seem worthy of presentation here. First, one important concept seems to have been lost sight of too frequently in the dispute between those favorable to the use of the fragility of the minute vessels by one method or another, and the chemically minded group, namely, that the vitamin C saturation or lack of saturation and the clinical disease, scurvy, are two different conditions. To enlarge: an individual may be on a vitamin C-free diet for a very long period of time without developing clinical scurvy, and yet, by chemical studies of the urine and blood, may reveal a marked condition of vitamin C unsaturation. Conversely, a patient with severe scurvy may show a rapid chemical response to the administration of large doses of vitamin C, yet still have evidences of the disease, scurvy. If the vitamin C dosage is continued, these will, however, quickly clear up. Schultz⁹⁰ in 1933, and the author,⁹⁵ in 1934, reported early studies of the effect of cevitamic acid on the "capillary fragility" in cases of scurvy and since, these authors and others have confirmed their observations, namely, that, in scurvy, the fragility of the minute vessels of the skin is increased and that the administration of cevitamic acid produces a return to the normal status coincidental to the cure of the disease. While the chemical tests, therefore, probably give the more accurate picture regarding the degree of vitamin C saturation of the body, it is our feeling that the fragility of the minute vessels is among the earliest signs of scurvy and response to cevitamic acid therapy can be well followed by careful observations of the capillary fragility.

It should be clearly understood that a number of conditions, such as thrombocytopenic purpura, poisons such as neoarsphenamin, and carbon monoxide, toxins such as those of scarlet fever and diphtheria, metabolic products associated with anemia and acetoneuria, menstruation, and others, may produce an increased capillary fragility. A history of low vitamin C intake, a high capillary fragility and a response to cevitamic acid therapy with a resultant return to normal figures is certainly significant and a common occurrence on the wards of Bellevue and Post-Graduate Hospitals. These tests have been criticized as being variable and not accurate within narrow limits. This might be said of many extremely important tests used in medicine and certainly of many chemical tests commonly accepted as helpful. Fluctuations of a few petechiae more or less are of slight significance, but, when a patient has 120 or more petechial spots with scurvy or a prescurbic condition (by the method reported⁹⁴) with a reduction to 12 to 15 petechial spots within 2 to 4 weeks of treatment coincidental with clinical cure, it would seem an important observation.

A disadvantage of the increased pressure method is that, by alternating arms, the tests can be done only about every 4 days, 8 days allowing time for healing of the ruptured vessels. On the other hand, large areas can be marked off for observation. Gothlin and his fellow workers use an area 6 cm. in diameter at the elbow crease. We feel that the skin below the elbow is more even in texture and in distribution per unit area of minute vessels, and have, therefore, used two circles each 2.5 cm. in diameter, the upper edges of which are 4 cm. below the elbow crease.

The average counts are used. Some of the unfavorable reports concerning the value of this phenomenon have come from workers using the negative pressure methods.^{110,112} Studies of the skin vessels during the past few years have demonstrated to us¹¹³⁻¹¹⁶ that the number of minute vessels, especially venules, present in different areas of skin varies very markedly. When a small suction cup 1 cm. or less in diameter is used over various areas of the extremities or the body, the results may be invalidated unless careful vessel microscopy studies are done first, to determine the presence of a large enough number of minute vessels to render a satisfactory test possible. This factor has not been considered in the reports of the above-mentioned workers. This objection is overcome when larger areas are studied.

A brief illustrative case report⁸⁴ may clarify the relationship of the chemistry to the capillary fragility. For many months the patient concerned and her husband lived on a total income of \$1.75 a week for food, and inquiry revealed the fact that during that time, practically no vitamin C containing foods were taken. She noticed a marked tendency for easy bruising and for hemorrhages to appear under her toe nails. (We have seen several patients in whom this symptom was prescotic.) About 2 months before admission to the clinic, she began to eat an orange about once a week and added a few other vitamin C containing foods to her diet rarely. On July 1, 1936, the capillary fragility test by the method we have described⁵⁶ produced 63 petechiae (0 to 10 being normal and 10 to 20 the upper marginal zone). This was definitely pathologic, but the 24-hour urinary excretion was 27.37 mg. and the blood level 0.95 mg. %, both normal. A complete blood count including platelet count was normal, and the sedimentation rate was 12 mm. in 60 minutes. A saturation test, injecting 1 gm. intravenously, produced a return of 873 mg., indicating a condition of satisfactory saturation. After 4 more doses of 1 gm. intravenously in 6 days, the capillary fragility test produced 22 petechiae which disappeared within 12 hours, while, after the preceding test, they were still plainly visible after 24 hours. Injection of a 2 gm. test dose intravenously produced a return of 92% (1842.4 mg.) in 24 hours, indicating a condition of marked saturation. She received a total of one dose of 1 gm. and one dose of 2 gm. in 7 days, and a capillary fragility test showed 30 petechiae. For the next 6 days, she took 1 gm. a day by mouth. At the end of that period, the fragility test produced only 12 petechiae, practically within normal limits. Her general condition had markedly improved. She no longer bruised easily, and no new hemorrhages appeared beneath her nails. We have now had occasion to study over 40 such patients, some of whom are reported in detail in a previous paper,⁵⁶ and the results closely parallel and confirm the observations of Schultzer,^{99a} Daldorf,¹⁰⁷ and others. Our explanation of the above case would be that, while her small vitamin C intake had been sufficient to raise her blood and urine figures to within a normal level, she had not yet recovered from her early scotic condition and that the massive doses of eevitaminic acid effected a rapid cure. Our past experience with such cases has been that abstinence from vitamin C rapidly results in an increase in the petechiae produced by the fragility test in contrast to a normal person, who is not so near the borderline of vitamin C deficiency.

A thorough understanding of the principles of crystalline vitamin C therapy must be dependent upon a knowledge of the fundamental considerations outlined above. We shall now survey the work thus far published dealing with its use in specific pathologic conditions.

The Use of Cevitamic Acid in the Treatment of Scurvy.—The disease, scurvy, was naturally immediately considered curable by crystalline vitamin C. Schultzer,^{99c} in 1933, reported the first cure by the use of vitamin C in man. During 1934, Wentzler,¹¹⁷ Neuman,¹¹⁸ Brugsch¹¹⁹ reported cures in children, and Wright⁹⁸ favorable results in the first 3 patients (adults) treated with this substance in this country. Since then, so much confirmatory work has been published by both these and other authors, that further comment regarding the curative effect of vitamin C in this condition seems unnecessary. Certain observations regarding scurvy may, however, be of importance. Although it has been erroneously looked upon as a rare disease in our modern civilization, workers who are interested and aware of its multiple and insidious manifestations find it rather commonly in all walks of life. We have found it as a result of various faddist diets, poverty, distaste for foods containing vitamin C, and inability to use vitamin C when taken by mouth, due to achlorhydria and other gastro-intestinal disturbances, hypersensitivity to citrus and other vitamin C foods, with resulting omission of these from the diet, and last, but not least, diets prescribed by physicians for the treatment of gastro-intestinal lesions, such as ulcers, colitis, and so on. The scurvy has in several instances been present and producing major symptomatology, while the patient was being cared for by the physician who prescribed the causative diet. It should be remembered that scurvy does not always begin in the classical way but the symptoms complained of may be hemorrhages under the toe nails (as reported above), bleeding from the bowels, easy bruising, small scleral hemorrhages and the more common bleeding from the gums, commonly confused with pyorrhea. Weakness and secondary anemia are often present. These symptoms, with a marked increase in the capillary fragility, and a history of a vitamin C low diet, should suggest the diagnosis. Complete clearing of the symptoms with a return to normal of the capillary fragility as a result of cevitamic acid therapy makes the diagnosis presumptive. Blood and urine studies should be looked upon as confirmatory, with the above mentioned limitations. They may, however, be of utmost importance in determining the condition of vitamin C unsaturation, a necessary precursor to scurvy. Plaut and Bulow⁵⁰⁻⁵² feel that the vitamin C content of the spinal fluid furnishes a more accurate index of vitamin C saturation of the body than do blood studies. It has been recognized for some time that anemia of a moderately profound type may be found in patients with chronic scurvy. This type of anemia responds quickly to the use of cevitamic acid and not to liver extract or iron.^{120,121} A definite reticulocyte response pattern has been reported by Faulkner.¹²²

The Use of Cevitamic Acid in the Treatment of Other Hemorrhagic Conditions.—It was logical that attempts should be made to treat other hemorrhagic conditions with large doses of this substance and certain workers, notably Boger and his co-workers^{123,124} and Engelkes¹²⁵ felt that the results were very satisfactory after its use in cases of

Schönlein-Henoch's purpura, hemophilia and thrombocytopenic purpura. We have been unable to satisfy ourselves after rather extensive studies reported in part⁵⁶ that cevitamic acid in dosage up to toxicity (5000 mg. intravenously) has any effect on the course of thrombocytopenic, Schönlein's purpura or hemophilia. It should be remembered that these conditions alternate periods of remission with periods of relapse. Following the patient through complete cycles, as we have done, demonstrates relapses during therapy. It should be noted that some patients with scurvy have low platelet counts, and there may be an increase in platelets along with the general response to vitamin C therapy. Certain of these patients and other hemorrhagic scurvy patients have undoubtedly been diagnosed as thrombocytopenic purpura or hemophilia in the past.

The Use of Cevitamic Acid and the Treatment of Gastric and Intestinal Ulcers.—The use of cevitamic acid in the treatment of gastric and duodenal ulcers has been the object of some study. Schultzer⁹⁹ studied the capillary resistance of 59 ulcer cases in comparison to 418 routine medical cases, as admitted to the hospital and found no appreciable difference. He concluded that vitamin C deficiency was not an etiologic factor in the production of peptic ulcer. We are not familiar with any evidence of importance to the contrary. On the other hand, in our own experience, we have been able to give antiscorbutic doses by mouth to acute ulcer patients without disturbance. This is important when fruit juices and the other sources of vitamin C are poorly tolerated, since the superposition of scurvy upon an ulcer syndrome is certainly not to be desired. It is doubtful that a hemorrhage from an ulcer could be affected by the administration of vitamin C, since such bleeding is usually from an eroded small vein or artery, while the action of cevitamic acid appears to be principally on the capillary venule and arteriole walls. That there are patients suffering from so-called colitis as a result of a prolonged abstinence from vitamin C, we are convinced. We have reported one such case in detail⁵⁶ and have seen two others. In addition, in certain patients with a colitis on another basis, but who have been on a vitamin C-low bland diet for a prolonged time, the addition of cevitamic acid to the diet may bring about marked improvement in their general condition and a decrease in the bleeding. This is especially indicated if an unsaturation of vitamin C is determined by the methods above reviewed. Similar results have been reported by Hetenyi.¹²⁶ As a preventive measure, 50 to 100 mg. per day may well be added to the diet. It appears to be non-irritating in such dosage.

The Introduction of Two New Anti-hemorrhagic Vitamins.—During the past 3 years, Dam¹²⁷ and his co-workers and Almquist and Stokstad¹²⁸⁻¹³⁰ have demonstrated the production of a hemorrhagic scurvy-like disease in chicks and its cure by the administration of a fat soluble substance occurring in hog liver fat, hemp seed and certain vegetables which they have termed anti-hemorrhagic vitamin K. Vitamin C is ineffectual in the treatment of this condition.

Another substance asserted to have a definite effect in decreasing the fragility of the capillary walls in certain conditions when ascorbic acid fails has been recently presented as a vitamin P by Rusznyak and Szent-Györgyi.¹³¹ They found it closely associated in the cell with

vitamin C. Chemically it appears to be related to the vegetable dyes, the flavenols. Work on these two new substances has not progressed far enough to determine fully their relationship to each other and to vitamin C, if, indeed, there is any.

The Relationship Between Vitamin C Metabolism and Rheumatic Fever and Rheumatoid Arthritis.—In interesting studies, Rinehart and his co-workers have attempted to establish vitamin C deficiency as one of the etiologic factors in the production of rheumatic fever and rheumatoid arthritis.¹³²⁻¹³⁴ In animals, they reported that infection with a beta-streptococcus produced no significant lesions on the heart valves in the presence of adequate nutrition. When lesions did occur, they were of an exudate type. In uncomplicated scurvy they found atrophic and degenerative changes in the collagenous stroma of the heart valves. In animals with scurvy plus added infection, lesions of a combined degenerative and proliferative character developed with considerable frequency, and, in the opinions of these authors, presented a striking similarity to the lesions of acute rheumatic fever. Schultz¹³⁵ and Mote,¹³⁶ while able to duplicate the production of similar lesions, felt that the changes only slightly resemble those of rheumatic fever. Rinehart points out that most of the rheumatic fever patients come from the underprivileged classes on an average low vitamin C diet and that, clinically, many of his patients gave a history of a low vitamin C intake or other evidence of vitamin C unsaturation. On the other hand, Schultz, Sendroy and Swift¹³⁷ and Shapiro¹³⁸ were unable to satisfy themselves that there is any clinical relationship between scurvy and rheumatic fever on the basis of previous dietary history or response to the giving of fairly large doses of vitamin C. We have been unable to affect the course of rheumatic fever cycles by giving cevitamic acid in doses as large as 1000 mg. or even 2000 mg. intravenously daily.⁸⁴ Rinehart does not feel that lack of response to vitamin C therapy necessarily disproves his contention, since scurvy may be only a factor in the preparation of the soil for the infection, but it would seem that the course of the disease should be ameliorated to some degree by the use of such large doses if there were a definite relationship. At present, however, it is possible to state only that further observations are necessary to clarify this important problem.

The Use of Cevitamic Acid in the Treatment of Tuberculosis.—It has long been recognized that patients with tuberculous were helped by the inclusion of large amounts of vitamin C in their diets. Animal studies have tended to confirm this.¹³⁹⁻¹⁴⁵ Recently, studies of man have appeared which demonstrate that there is an increased vitamin C requirement in this disease,^{146,147} and that there is a rough parallelism between activity of the disease and the daily excretion of cevitamic acid on a controlled diet.¹⁴⁵ Heise and Martin¹⁴⁴ do not include in their brief report the relationship between the vitamin C excretion and the degree of fever, which, in turn, usually does parallel the activity in tuberculosis. We have found that fever from various causes increases vitamin C metabolic demands,⁸⁴ and it would seem that this may be the primary factor in their studies rather than tuberculosis as a specific disease. This point should at least be clarified. (One exception to this finding has been reported to be malarial fever.¹⁴⁹) Steinbach¹⁵⁰ and his co-

workers are at present engaged in studies of the effect of vitamin C on intestinal tuberculosis in man. Preliminary observations on a small series (9) seem to indicate a definitely favorable response with a halting of the usual downward course, gain in weight in 4 cases, and a striking improvement in the hemoglobin and red cell count in all 9 patients. This approach should be critically studied at greater length. It is too early to estimate the value of such treatment at present. Massive dosage (1000 to 1500 mg. daily) might well be tried. A question which naturally arises is whether the deposit of vitamin C in the intestinal wall which is one of the storage centers of the body plays a part in the effects in this specific group of cases.

The Metabolism of Vitamin C in Pneumonia.—It has also been found that there is a definite diminution in the urinary excretion of vitamin C during pneumonia,¹⁴⁷⁻¹⁵¹ and that this can be compensated for by the use of cevitamic acid in large doses. It is tolerated better than citrus fruit juices which in large quantities produce gas and often diarrhea. No correlation has been found between the clinical condition of the patient and the vitamin C excretion, but this seems rather to follow the fever curve and, in our opinion, is more likely associated with the increased metabolism than the specific disease, pneumonia. Although suggested by Hockwald,¹⁵² there is at present no conclusive evidence that the course of pneumonia is affected by the administration of vitamin C in any form.

The Effect of Cevitamic Acid on Pigmentation.—The effect of cevitamic acid on cutaneous pigmentation has been studied with resulting divergence of opinion. Szent-Györgyi¹⁵³ and Szüle¹⁵⁴ reported a definite amelioration of the pigmentation associated with Addison's disease. The regression of cloasma has been reported by Sellei¹⁵⁵ and the diminution in the pigmentation from sunlight was claimed by Schade.¹⁵⁶ On the other hand, Teelner¹⁵⁷ failed to confirm the effect on cloasma (using lemon juice), and Drigalski¹⁵⁸ concluded from his studies that the pigment produced by ultraviolet radiation is not influenced by vitamin C. Hoff¹⁵⁹ feels that there are three possible pathological causes for skin pigmentation: hormonal, neurovegetative and vitamin C deficiency. He suggests that the pigmentation of Addison's disease may be due to an avitaminosis C of endogenous origin. He reports encouraging results in patients with pigmentation due to Addison's disease, known vitamin C deficiency and in certain cases of undetermined etiology. It is obvious that much further study is necessary to clarify this situation, but the trial of cevitamic acid for certain types of pigmentation seems justified in the light of our present knowledge.

The Relation of Vitamin C to Diphtheria Toxin.—Considerable experimental work with animals has established a relationship between vitamin C and diphtheria toxin¹⁶⁰⁻¹⁶² and v. Gagyí showed that very similar changes in the ovary, posterior lobe of the pituitary gland and adrenal cortex occur in diphtheria toxin intoxication and scurvy.¹⁶³⁻¹⁶⁶ In guinea pigs, the action of diphtheria toxin can be overcome by the administration of adrenal cortex and cevitamic acid, while either of these agents alone fails to be effective.¹⁶³⁻¹⁶⁸ Clinical studies reporting encouraging results in the treatment of diphtheria on the same basis have been reported, the clinicians confirming the need for the use of

adrenal cortex plus cevitamic acid, whereas insulin is contraindicated.¹⁶⁹⁻¹⁷¹ This, of course, must not be considered as a substitute for antitoxin therapy but merely supplementary to decrease the toxicity. The number of cases is too small and too poorly controlled to establish this as more than experimental therapeutics at present.

The Effect of Cevitamic Acid on Poliomyelitis Virus.—The work with diphtheria toxin led Jungeblut¹⁷² to investigate the effects of cevitamic acid on poliomyelitis virus *in vitro* with the following significant findings: 1, extraordinarily small amounts of vitamin C are capable of rendering non-infectious multiple paralytic doses of poliomyelitis virus as determined by the intracerebral injection into rhesus monkeys; 2, the quantitative aspects of this inactivation are remarkably similar to the neutralization of diphtheria toxin by vitamin C; 3, vitamin C in the form used in these tests is a normal constituent of various animal and human tissues, particularly adrenal and brain, and occurs in a reversibly oxidized state in the blood. Our present figures for vitamin C content in the central nervous system are within the range found to be neutralizing. Studies should be made to determine whether there is a variation in these figures between susceptible and non-susceptible individuals. Studies to determine therapeutic or prophylactic possibilities are under way.

The Effect of Cevitamic Acid on General Infections.—While it has been frequently stated that vitamin C is indicated as a preventative and therapeutic agent for infections, generally, it should be noted⁸⁴ that, under our observations, patients who have been completely saturated, having been for many days on dosages as high as 1000 mg. intravenously per day, have developed acute infections such as tonsillitis, otitis media and abscesses.

The Relation of Vitamin C Metabolism to Diabetes Mellitus.—Studies on the vitamin C content in the urine of diabetic patients have failed to reveal any relationship between the degree of diabetes and the vitamin C content of the urine.

The Relation of Vitamin C to Dental Problems.—Lack of vitamin C, as indeed most of the known vitamins, has been considered as a possible factor in the production of dental caries. Howe showed in 1920 to 1923 that, by feeding guinea pigs a scorbutic diet, he could produce all of the better known dental lesions, including alveolar resorption, spongy gums, pockets and pus formation, together with caries and irregularities in the teeth themselves.¹⁷¹ On the other hand, Mellanby¹⁷³ could not duplicate this work using puppies. Comment on these divergent reports is necessary. The guinea pig differs from the dog (and man) in its persistent tooth growth. Each tooth, at a given moment, shows all stages from the embryonic through maturity to senility and degeneration. This cycle takes about 40 days. Dogs, however, do not represent satisfactory experimental animals for this study, since they (unlike humans, monkeys and guinea pigs) do not need vitamin C, being able to synthesize it in their body. Fish and Harris¹⁷⁴ in careful studies, using guinea pigs, found that in every case where deprivation of vitamin C was severe enough to produce results observable by histologic methods, it was found that odontoblasts, ameloblasts, cementoblasts, osteoblasts, osteoclasts and bone corpuscles had undergone complete degeneration

and were sometimes completely destroyed. Dalldorf and Zall¹⁷⁷ had previously found that vitamin C deficiency retarded the tooth growth in guinea pigs. This work needs confirmation in monkeys and man. We know, however, that spongy, bleeding gums are frequently due to vitamin C deficiency, and, when on that basis, will yield to cevitamic acid therapy. Hanke¹⁷⁸ has presented evidence that the regeneration of bone after fractures can, in most cases, be hastened by the administration of cevitamic acid.

The Relation of Cevitamic Acid to Goiter.—Cevitamic acid and its effect on thyroxin have been recently studied, but again the reports are confusing, although the work is not strictly comparable. Demole and Ippen¹⁷⁹ reported that the lethal thyrotoxic effect of thyroxin on guinea pigs can be counteracted by cevitamic acid. On the other hand, Spence and Seowen,¹⁸⁰ using cevitamic acid, could find no evidence of prevention or diminution of the thyroid hyperplasia in guinea pigs following injections of the thyrotropic hormone of the anterior pituitary. On the basis of this and other studies, they conclude that cevitamic acid is not an antigoitrogenic substance.

Dosage.—Cevitamic acid has been administered orally and intravenously and will shortly be available for intramuscular use.¹⁸¹ Hitherto, it has been possible to use it intramuscularly, only if neutralized immediately before administration with sodium bicarbonate.¹⁸² Otherwise, there was grave danger of the production of a slough. The dosage is not finally determined; under normal circumstances, 30 to 50 mg. per day by mouth appears to protect an adult against scurvy, and we have given as high as 5000 mg. intravenously before obtaining toxic effects.⁸⁴ Dosage should, then, be between those limits and should depend on the rapidity of the action desired. Probably 1000 mg. per day should be considered the maximum dose except under very unusual circumstances.

General Summary.—It is clear from the above review that the discovery of crystalline vitamin C has opened up a new and enormous field for laboratory and clinical research. It at once becomes apparent, as is usual under such circumstances, that much of the early work is confusing, and even conflicting in its results. Time and further studies will separate the grain from the chaff. At present, few general statements can be made with any finality in this particular field. It is fairly certain that cevitamic acid is of definite value in the treatment of patients who are suffering from vitamin C undernutrition, especially where rapid response is desired or where rich food sources of vitamin C cannot be utilized, because of gastro-intestinal disease, hypersensitivity or lack of utilization when taken by the oral route. We have come to realize that the manifestations of vitamin C deficiency are far more variegated than we formerly considered possible, under the classical syndrome of scurvy, and that these manifestations are present in considerable frequency in our present civilization. Cevitamic acid will probably have an increasing use as more of these manifestations are recognized. At present, the debatability of its use in any condition seems to be in reverse proportion to our certainty of the relation of that condition to vitamin C deficiency.

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RADIOLOGY

UNDER THE CHARGE OF
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AND

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Lesions Involving the Cranium and Its Contents.—In a comprehensive review of the history of radiologic diagnosis, Percy Brown stated that the early roentgenologic studies of the skull were unsatisfactory if not, indeed, discouraging. To pioneer workers in this field, he pointed out, were presented the same difficulties here as in other regions possessing three dimensions of nearly the same extent. As the handicap of required penetration was gradually overcome, there remained the real problem of differentiating tissue changes within superimposed structure of itself relatively dense. While attempts were made as early as 1897 to apply roentgenography to the study of intracranial tumors, Brown stated that Schüller, as late as 1917, considered the problem of differentiating tissue changes in the skull, in less experienced hands, constituted the unattainable, and that it required the wisdom of experience to realize that only occasionally could such information be obtained directly.

Two factors that had considerable to do with the progress of subsequent years were the introduction of the Potter-Bucky diaphragm (1916) and the modern duplitized Roentgen ray film (1918). The former with its suppression of secondary radiation and the latter with its reduction in exposure time when used with double screens afforded the brilliancy of detail in the roentgenogram necessary to the recognition of the finer changes of density in bone or in the tissues of the cranial contents.

In 1918, the procedure of ventriculography following the injection of air into the lateral ventricles, performed by Dandy and developed roentgenotechnically by Baetjer was accomplished. In his announcement, Dandy (1918) declared that these structures could be sharply outlined if air was substituted for cerebrospinal fluid, leading to the diagnosis and localization of many intracranial conditions; in internal hydrocephalus, he found the procedure invaluable. A few months later Dandy reported a simpler, less dangerous method of accomplishing the same object to which he gave the name encephalography. In ventriculography, gas or air was introduced into the ventricular system by means of direct ventricular puncture through trephine openings. In encephalography, gas or air was introduced into the ventriculo-subarachnoid space through subarachnoid puncture at the cisterna magna or lumbar sac. Each has its specific indications and contra-indications.

The consensus of opinion expressed by various authors would indicate that brain tumors can be localized without the aid of roentgenographic methods in 50% of cases. A definite proportion can be localized from the roentgenographic findings. In the remaining group, ventriculography and encephalography is the combined effort of the neurologist, the roentgenologist and neurosurgeon.

Lesions of the skull are, with a few exceptions, quite similar to those of other bones of the body, Sosman (1927) stated, while those arising in the brain, its coverings and appendages, are not duplicated elsewhere in the human anatomy. As bony tissue, the cranial vault is liable to injuries, anomalies and deformities; inflammations and repair; and new growths, both primary and secondary. Anomalies of the skull, especially as to size and shape, are rarely of importance, unless one classifies turriccephaly, scaphiocephaly, oxycephaly, and so on, under this heading. These would better be grouped under the heading "synostosis crani" which indicates that the trouble is due to early closure of the sutures, with a consequent marked increase in intracranial pressure as the expanding brain pushes against the unyielding skull.

Primarily, one thinks of brain tumor or other intracranial lesion when roentgenographic examination of the head is requested. Not infrequently the findings are those of lesions other than intracranial. Pendergrass and de Lorimier reviewed the lesions found involving the calvarium, that portion of the skull above a plane drawn through the supraorbital ridges and the superior nuchal lines of the occipital bone. A knowledge of these lesions, particularly the osteolytic, is necessary to avoid erroneous interpretations of more serious lesions. They illustrated several common or anomalous developmental conditions

such as dysostosis of the cranial bones, found in association with absence of or defective development of one or both clavicles (cleido cranial dysostosis); partial dysostosis, almost always the result of an interfering meningocele; vascular pools in the diploë spaces and particularly in the anterior or posterior parietal regions, occasionally with erosion on the inner aspect of the internal table due to pockets of the meningeal vessels or even of the venous sinuses; and Pachionian depressions producing erosions of the internal aspect of the inner table and confined to the parasagittal regions. Filling defects may result in bone from: erosions by lesions essentially extraosseous, such as malignant neoplasms of the scalp, epitheliomata or sarcoma cutis; pneumatocoele, pockets of air located either just beneath the scalp or confined within the cranial vault; angiomas of the meningeal vessels, "spider-like" elongated tortuous channels of erosion or a widespread plexus erosion "angioma racemosum;" dilated emissary vessels in the occipital region near the midline; aneurysm of the cerebral vessels in the basal portion of the skull or in the occipital region; cerebral neoplasm, primary or secondary, situated superficially; hydatid cyst in the cerebral cortex; and pencephaly, due to relative herniation of regional portions of a lateral ventricle in superficial atrophy of the brain substance, following birth injuries or trauma subsequently incurred.

Bone destruction due to a lesion actually present between or within the tables of the skull included: ancient traumatic or surgical fenestrations; metastatic malignant lesions; plasma cell myeloma; endothelial myelomata; chloroma; xanthomatosis; cholesteatoma (epidermoid or dermoid); Hodgkin's granuloma; osteomyelitis (non-specific, syphilitic, yaws, tuberculosis, mycotic, kala-azar); mucocoele; and meningioma. Pepper and Pendergrass added an anomaly of development of the parietal foramina in the upper posterior angle of the bone. Rarely, foramina of large size result, apparently from an irregularity in the process of ossification, and these may be misinterpreted as xanthomatosis or any one of a number of the above mentioned defects. The anomaly is hereditary, in one family it was traced through 3 generations. Sosman (1935) listed osteoporosis, osteoporosis circumscripta, osteomalacia, osteitis fibrosa cystica, osteitis deformans (Paget's disease), and leontiasis cranii and bone changes associated with endocrine deficiency or dysfunction in addition to the lesions above mentioned and added osteogenic sarcoma, hemangioma and osteochondroma to the primary tumors involving the skull.

In a review of approximately 3000 roentgenograms of the skull, Dyke (1930) noted a thickening and irregularity of the inner table of the frontal bone, commonly designated as a benign or senile hyperostosis, in 3.7% of the series. Sherwood Moore studied the series of roentgenograms made on 6650 patients and found 96 similar lesions which he termed hyperostosis frontalis interna. He also found 133 cases where the abnormality was limited to the diploë; the tables were unaffected. He termed the latter nebula frontalis, hyperostosis calvaria diffusa and hyperostosis frontoparietalis according to their location. Roentgenographically they showed a cloudy effect typifying a general even increase in the volume and density of the diploë of the vault.

The four types exhibited regional distribution, all were bilaterally symmetrical, and all four or any combination of the four occurred in one individual case. In his series, the patients, approximately 98% women, with but few exceptions, revealed a symptom complex as striking as the Roentgen findings. All were obese, or showed a tendency to obesity of the rhizomelic type. This, with hirsutism, usually on the chin, less frequently on the upper lip, suggested an endocrine factor. Headache, frequently disabling and referred to the forehead, with occasional tenderness and a feeling of pressure was a striking symptom. Other neurological findings were listed as noted in various patients or groups of patients showing these bone changes.

Dyke (1930) observed in 4.5% of his series a normal perpendicular bone formation in the outer table of the skull, usually in the parietal region, which as he remarked exhibited some of the characteristics of and might be misinterpreted as sarcoma, meningioma or bone changes seen in some of the congenital anemias of children. Meningioma (dural endothelioma, endothelioma of the meninges, sarcoma of the dura) may appear as a cranial hyperostosis in the roentgenogram. Phemister credits Virchow with the first report of an endothelioma with overlying hyperostosis. The usual interpretation was that the growth of the underlying tumor stimulated the overlying bone, leading to non-tumorous new bone formation. It was found by histologic study the tumor was primary in the meninges and invaded the bone by direct extension. Cushing (1922) presented the first extensive series studied by a single observer with much general information of the subject, especially as to the frequency of occurrence and the localization of the hyperostoses and the types of intradural lesions producing them. Sosman and Putnam grouped the various meningiomas of their series and stated the proportion of each recognizable on the roentgenogram. The types were: 1, The cranial-nerve-foraminal tumors; 2, the suprasellar tumors; 3, tumors arising from the olfactory groove of the ethmoid; 4, sphenoidal ridge tumors; 5, Sylvian cleft (temporo-frontal) tumors; 6, tumors of the convexities; 7, parasagittal meningiomas; 8, meningiomas of the falx; 9, tumors of the transverse and sigmoid sinuses.

When the meningioma presents as a hyperostosis it may show as either an increase or a decrease in the density of the bone; as an erosion characterized by a localized roughly circular area of thinning with a mottled spongy appearance, irregular in outline, surrounded by small wormlike vascular channels radiating from the eroded area and frequently disappearing in small circular holes where the vessels perforate the bone; or as osteomatous changes, nearly always associated with erosion and vascularity, usually as spicules of bone running perpendicularly to the surface of the bone, or occasionally as a diffuse thickening of the involved bone. In about 25% of their cases the channel for the middle meningeal artery was enlarged on one or both sides, depending on the location of the tumor. This is also found with other tumors and occasionally similar vascularity is found without any demonstrable lesion.

Neurinomas (acoustic nerve tumors) were rarely recognizable as such in Sosman's series, but frequently gave general signs of increased

pressure and occasionally caused erosion of the petrous bone evident as a unilateral enlargement of the internal auditory meatus. Towne reported a technique developed by Chamberlain to show this erosion, and reported 3 cases in which the lesion had been demonstrated by the Roentgen ray. Camp (1929) found that normally there may be a considerable difference in the diameter of these openings in the same skull and considered localized erosion of the petrous portion of the temporal bone and the adjoining base of the skull as reported by Pancoast and Mayer a more reliable sign. Taylor and Geyman and Clark discussed the use of various positions to demonstrate suppuration of the petrous pyramid. Sussman described an apparatus for making simple exposures of the petrous pyramids in the Stenvers projection and modifications of this technique to show the mastoid process, mastoid antrum, tympanic ossicles, labyrinth, internal auditory meatus and middle fossa of the skull.

In a review of approximately 3000 roentgenograms of the skull, Dyke (1930) noted the frequency of what are generally regarded as "physiologic" intracranial calcifications. He found calcification within the pineal gland in 51% of his series. Naffziger and Vastine and Kinney devised methods of measuring the normal position of this gland and using deviations from this normal position as an indirect method of locating brain tumors. Frontal tumors displaced the gland posteriorly, temporal tumors also caused posterior displacement, parietal tumors displaced the gland downward, occipital tumors displaced it anteriorly. Unusually large tumors also displaced the gland in other directions. The subtentorial tumors caused varying degrees of upward displacement. Only very large intrasellar or extrasellar tumors displaced the gland, then posteriorly. Tumors generally displaced the gland to the side opposite the neoplasm, cicatricial contraction in old inflammatory lesions drew the gland to the affected side. Dyke found calcification of the choroid plexus in 5.1% of his series. This was bilateral and symmetrically located and offered little chance of confusion with the pineal. Calcification in one or both of the internal carotid arteries was seen in only 1.3% of his cases. Ossifications in the falx cerebri were noted in 6.9%. O'Sullivan found these usually in the anterior portion in the form of needles, plates or buttons which are at times paired in the two layers. These so-called osteomas of the falx are also seen in the tentorium cerebelli, especially in the region of its attachment to the dorsum sellae and the crest of the petrous portion of the temporal bone, also in that strip of dura which forms the periosteum of the clivus, the bony surface which slopes down from the pituitary fossa. He reported retrobregmatic ossifications of the dura which he had not before seen described.

Pathologic calcification may occur in tumors, hematomas, tubercles, aneurysms, old abscesses, areas of old meningeal disease and encephalitis. Camp (1930) divided these for practical consideration into the neoplastic and non-neoplastic groups. Of the neoplastic group, calcification was most common in the glial tumors (arising from the brain tissue), endotheliomas (meningiomas), suprasellar cysts (Rathke's pouch tumors), hemangiomas, dermoids, and cholesteatomas. Other tumors rarely calcified. The gliomas, which made up 43% of Sosman's

series, showed only 10 to 12% calcified. Camp in his series found only 5%. Schwartz found calcification to vary according to the type of tumor. The calcification had a tendency to a string-like formation and involved a considerable area. Calcification in meningiomas occurred in two different areas: 1, within the capsule or membrane surrounding the tumor, and 2, within the tumor itself. In the first instance the shadows of the calcification closely simulate those of the calcific or osseous plaques found in the falx or meninges; in the second instance there were punctate and discrete areas of density corresponding to the psammoma bodies which these tumors frequently contain or conglomerate masses of calcareous material. Suprasellar cysts showed calcification of some degree in 70% of Sosman's series. The calcified shadows, seen about the outlet of the sella turcica, above the clinoid processes, posterior to the clinoid processes, and even within the sella turcica itself, are often of a faint, irregular flocculent nature that may be easily overlooked. In many cases a dense calcified mass with indistinct edges was observed. The walls of the cyst may calcify in a linear fashion. Calcification in dermoids and cholesteatomas simulate those of Rathke pouch tumors very closely. In the non-neoplastic group, aneurysms containing calcium sufficient to render them opaque to Roentgen rays are rare; where demonstrable the shadows are seen above or just lateral to the sella turcica. Unilateral erosion of the sella turcica or clinoid processes may accompany the lesion. Angiomatous malformations, venous and arteriovenous, are primarily surface lesions of the hemisphere; in the roentgenogram the shadows closely simulate diffuse calcification of an atrophic cerebral cortex. Calcification in hematomas was largely confined to areas within the substance of the brain, visualized as an irregular dense shadow, roughly triangular in shape. Subdural hematomas rarely have a calcium content sufficient to make them demonstrable on the roentgenogram. Changes in the sella turcica are an important roentgenological manifestation of intracranial disease. Camp (1923) dissected and made tracings of 110 sella turcicas and reported his findings graphically. His findings were similar to those of other observers quoted, that there was a wide variation of the normal. The same author, in 1924, stressed the necessity of an adequate roentgenographic technique to avoid misinterpretation of the findings. Bridging of the sella was rare in his experience and of no clinical import. Intraseilar tumors enlarge the sella in a uniform circular manner at the expense of the floor and the dorsum sellæ. The floor is slowly eroded until a pouching into the sphenoidal sinus occurs with total destruction of the intervening bone. The roentgenogram shows a double line of the floor, the higher line representing the lateral border of the pituitary fossa, the lower is produced by the contrast of the air in the sphenoidal sinus against the lower border of the tumor. The dorsum sellæ is thinned and eroded; it first becomes concave on the anterior surface, later straight and narrow, and finally is pushed backward by the increasing size of the tumor. The anterior clinoid processes are not affected until the tumor has reached a fair size; when involved, they are usually eroded from below and behind with the production of short blunt processes. The amount of sellar deformity was no index to the extent of acromegalic changes elsewhere in the body.

The pressure associated with extrasellar tumors produces a widened and flattened sella. The posterior clinoids are eroded from above rather than anteriorly, and they become shortened and pointed rather than narrowed and thinned. The anterior clinoid processes are thinned and pointed rather than shortened and blunt. The posterior clinoids, owing to erect position and central location, are more easily eroded than the anterior, and in cases of marked intracranial pressure may exist only as mere remnants of the original structures. As the anterior wall of the sella and the tuberculum sellæ are eroded from pressure coming from above, the outlet of the fossa becomes widened and the depth is diminished. Unilateral lesions showed more marked destruction on the side corresponding to the lesion in the specimen, but these changes were not distinguishable on the roentgenogram. In children, pressure erosion will produce a "cupping" of the floor; if a large sphenoidal sinus exists the pressure produces complete erosion of the floor. Hydrocephalus induced by causes other than cerebral neoplasm, because of its accompanying increased intracranial pressure, will produce changes in the sella exactly simulating those induced by extrasellar tumors. Deformities of the sella produced by increased intracranial pressure resulting from such lesions as brain abscess, cerebral aneurysm, or craniostenosis (oxycephaly) cannot be differentiated in the roentgenogram from a deformity produced by other extrasellar lesions. Diseases of the sphenoid bone, either primary or secondary in origin, produce a marked change in the roentgenographic appearance of the sella.

When the neurological examination conducted by an experienced observer with a careful history, inspection of the visual fields and roentgenographic examination has failed to localize a lesion, ventriculography or encephalography, as the neurological findings indicate, is the method of choice. This procedure is necessarily a cooperative effort of the neurologist, the roentgenologist and the neurosurgeon, because in many cases it is but one step in surgical intervention, the operative procedure determined by the findings on the pneumogram.

In the radiological literature, Grant presented one of the most succinct reviews of the normal anatomy and physiology of the cerebrospinal fluid channels, a knowledge of which he considered essential to an intelligent interpretation of the pneumogram. Within each cerebral hemisphere lies a circumscribed collection of fluid, the lateral ventricle. On the floor of the ventricle lies the fluid-producing mechanism—the choroid plexus. Each lateral ventricle extends in three planes, arching forward into the frontal lobe (anterior horn), backward and laterally into the occipital lobe (posterior horn), and curving laterally downward and again forward into the temporal lobe (inferior horn). That part of the ventricle from which these horns extend is known as the vestibule and it is in this part that the lateral ventricle is largest. Roughly, the vestibule lies 3 cm. posterior to a line drawn perpendicularly over the vertex from one external auditory meatus to the other and at a horizontal level to this line and 5 to 7 cm. above the meatus. The two lateral ventricles are normally symmetrical and equal in size and shape. The only exit for the cerebrospinal fluid formed in each lateral ventricle is through the paired foramina opening from the lower median surface of the anterior horns, about 2 cm. behind their tips, the foramina

interventriculare (foramina of Monro). These foramina lead into the third ventricle, which lies directly in the midline, just above and behind the sella tureica and the posterior clinoid processes. From the third ventricle, the fluid passes down the midline through the aqueduct of Sylvius to the fourth ventricle. From the fourth ventricle the fluid is poured into the subarachnoid spaces through the medial foramen of Magendie and the two lateral foramina of Luschka. Thence it is carried up over the cortex to be reabsorbed into the blood stream along the vascular channels. The course of the cerebrospinal fluid is from within the lateral ventricles outward. Intracranial tumors cause two main types of changes in the outline of these ventricles, symmetrical and asymmetrical variations in their size, shape and position. Asymmetrical variations are due to tumors lying within the cerebral hemispheres lateral to the midline. These effects are due commonly to direct impingement on the lateral ventricles by the tumor mass. Symmetrical dilatations of the ventricles are due to obstruction of the free circulation of the cerebrospinal fluid, by tumors situated in the midline between the cerebral hemispheres, impinging on the foramina of Monro or the third ventricle, or in the posterior fossa blocking the aqueduct of Sylvius, the fourth ventricle or the cistern. In the roentgenogram the antero-posterior and postero-anterior projection, as a rule, furnishes the most decisive information. Defects in ventricular outline seen from these angles are much more likely to be real and not due to errors in technique. A shift in the position of the lateral ventricles, disproportionate or uniform changes in their size or shape, or obstruction of a horn, or of the entire ventricle, are easily discernible. The situation and size of the third and fourth ventricle may be noted. The lateral projections should confirm the findings in the sagittal plane observations. In interpreting the shadows seen on the lateral projections one must remember that the size of the posterior horns of the lateral ventricles show much variation; a complete absence of these horns may not be abnormal. A distortion must be observed in all projections to be of diagnostic value.

Torkildsen and Pirie constructed a cast of the cerebral ventricles and in a series of diagrams they illustrated the superimposed portions of the lateral ventricles as they appear on the roentgenogram on the anteroposterior and posteroanterior projections.

The advantages and disadvantages of the various methods suggested and used in the procedure of encephalography were discussed by von Storeh and a new simultaneous replacement apparatus was described, based on a clearer conception of the dynamics involved. The seeming complexity of the apparatus itself was more than balanced by the ease of operation and the results obtained. The advantages claimed were that the normal intracranial pressure was resumed when the patient was returned to bed; reactions were therefore less severe and the roentgenograms were more accurate. Freeman reported the use of colloidal thorium dioxide for ventriculography in about 20 cases over a period of 2 years. Advantages were that it was freely miscible with the ventricular fluid, permitting ready diffusion throughout the cavities. It was also of high specific gravity, tending to reach the dependent points in the ventricular system, and outlined the aqueduct and fourth

ventricle. Most important was the pressure relationships within the cranial cavity were not disturbed. In no case was more than 6 cc. of the thorium dioxid used. In cases where the fluid pathways were clear it passed readily to the subarachnoid spaces and was eliminated within 4 hours from the cranial cavity, at least in amounts detectable by the Roentgen ray.

Many excellent papers have been written on the interpretation of the pneumographic findings and others correlating the pathologic findings with the alterations from the normal observed in the roentgenograms. Those reviewed are included in the bibliography as a guide to a more intensive study of this increasingly interesting subject.

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ORIGINAL ARTICLES.

HEMOPHILIA IN THE NEGRO.*

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It is questionable whether true hemophilia exists in the negro race. In 1911, Bulloch and Fildes¹ presented their exhaustive monograph in which they announced the ability to trace all but six of the papers on this hemorrhagic diathesis existing in the literature of the world. Preceding this paper there were but 3 reports of alleged hemophilia in the negro. Since 1911 there have appeared no further accounts of its occurrence in that race.

The 3 existing accounts of hemophilia in the negro appear in abstract in the following paragraphs along with a brief discussion as to their merits as instances of this disease.

In 1874, there appeared in the "Clinic" of Cincinnati the presentation of the first report. Dr. Hadlock² described bleeding in a mulatto boy aged 7 years. The bleeding occurred from the gums at the base of a loose decayed tooth. Removal of the tooth caused an increase rather than the expected cessation of the hemorrhage. Persulphate of iron pledgets were applied to the bleeding socket with little effect. Silver nitrate locally and astringents internally were likewise of very temporary value. Following this a series of astringents and styptics was used to no avail, for the boy died from exsanguination 48 hours later. Dr. Hadlock mentioned no laboratory studies. He stated that there had been many deaths in this boy's family due to hemorrhage occurring from slight wounds. It was

* This paper was presented before the section on General Medicine at the College of Physicians of Philadelphia, on May 25, 1936.

more specifically noted that an uncle died as a result of hemorrhage from a cut with a scythe, and that the father of the boy bled to death following a briar scratch. Two brothers died of tuberculosis. There was no mention of a bleeding tendency among females in this family. This appears to be an example of true hemophilia but the presence of white ancestry in the mulatto excludes this case from a consideration of hemophilia in the negro.

The next instance of the disease in a negro was reported by Dr. W. R. Steiner³ in 1900. His patient was a negro girl aged 14, who was admitted to the hospital with hemorrhage from the nose and mouth, and headache. Her past medical history stated that she had bled easily from the slightest scratches since early childhood but that the amount of blood lost has been slight in every instance. There had been no epistaxis previous to the present illness. The present illness began 2½ months before admission when the patient lost about a cupful of blood due to a spontaneous nosebleed. Following this she felt weak and drowsy until her entrance into the hospital. Five days and 2 days before the admission epistaxis recurred.

There were herpetic lesions on the lower lip and over the clavicular areas. Three days after admission the gums were swollen and bled easily and purpuric spots appeared on the arms and legs.

The family history states that a brother had had a painful, swollen ankle joint following acute urethritis. The diagnosis was gonorrheal arthritis but Dr. Steiner suggests a possible hemarthrosis due to hemophilia. Six other brothers suffered occasionally from epistaxis and bled considerably from slight cuts and bruises. One died at the age of 34 of hemorrhage from the nose and mouth. There were 3 sisters who were not disturbed by a bleeding tendency. The mother bled from the nose at intervals until she was 16 when the bleeding tendency ceased. The grandmother occasionally bled from the nose and died at the age of 60 years from asthma, dropsy, Bright's disease and heart disease. The great-grandmother was a bleeder from childhood but, despite semi-annual cupping and leeching, she survived to die of old age.

The coagulation time on this patient was 3 to 4 minutes and the platelet count 212,000 per c.mm. No other laboratory studies were mentioned.

This is an instance of alleged hemophilia in a negress. Hemophilia probably does not occur in this sex despite numerous reports. Bulloch and Fildes found no typical example of hemophilia in the female in over 900 cases of the disease. Muir⁴ traced the genealogy of a hemophilic family through 7 generations including over 600 members and concluded that there was no greater tendency to bleed among the women of this family than in an equal number of women having no hemophilic connections. During the period from 1922 to 1936 there have been 12 patients with alleged hemophilia admitted to this hospital. All were in white males. But 5 of the 12

case histories bear careful scrutiny as to the accuracy of the diagnosis.

Steiner's case emphasizes the fact that when viewed over a period of several generations, some members of a given family are apt to display instances of hemorrhage. The family history in his case can scarcely be construed as that of hemorrhagic diathesis. The history, the physical findings of purpuric spots and hemorrhage from the gums, and a normal coagulation time seem to place this patient in the category of purpura, possibly of the familial or anaphylactoid type.

The third instance of hemophilia in the negro was that of a report of 2 cases by Dr. Louis Buck,⁵ of Portland, Oregon. His first case occurred in a negro male 30 years of age, who came to Dr. Buck suffering from spontaneous epistaxis. The nasal passages were packed with gauze, a posterior nasal pack was placed and calcium chloride 10 grains administered every 3 hours. The bleeding ceased and there was no further trouble. No laboratory findings, family history or past history were given.

His second case was that of a negress 24 years of age. She likewise presented severe epistaxis which was treated by gauze nasal packs. These packs were left in place for 7 days and the hemorrhage thereby controlled. No further episodes occurred. Here also no laboratory findings, family history or past history were noted. These 2 case reports of severe epistaxis warrant little discussion as instances of true hemophilia. It seems logical to suppose that there was little in the past history to suggest bleeding episodes and hemophilics seldom reach the third decade of life without some serious hemorrhagic manifestations. Furthermore one of these patients was a female.

Thus there is apparently no instance on record of hemophilia in the full blooded negro. The following example of hemophilia is therefore thought to be of sufficient interest to warrant its report.

Clinical History. The subsequent remarks concern a colored boy, J. B., aged 10 years.

His family history states that he has 4 siblings: a sister aged 6 years, who is living and well, another sister who died at the age of 1 year of diabetes, and 2 brothers, 13 and 6, who are living and well. Both brothers have nosebleeds on the average of once a week. Their bleeding times (Ivy method) were $4\frac{1}{2}$ and $2\frac{1}{2}$ minutes respectively. Coagulation time (capillary tube) 3 and $3\frac{1}{2}$ minutes; platelets (Olaf's method) 238,000 and 480,000 (May, 1936). The father is living and well and has no tendency to bleed. The mother is living and well, and in her family there are 9 brothers, all of whom are in good health and in which there is no history of bleeding except in the youngest, now 25, who has had frequent nosebleeds since childhood but no tendency to hemorrhage from cuts and no swollen joints. The patient's grandfather on the maternal side had frequent nosebleeds during the last few years of his life, but died of hypertension at the age of 76. There were no known bleeders among the mother's uncles. The mother of the patient has 6 sisters among the families of whom there is a total of 18 sons, all of whom are living and well and none of whom display a hemorrhagic tendency.

The mother, when questioned concerning interbreeding with the whites, stated that her grandmother (paternal) was a very black negress; her father and mother were likewise very black. Brothers and sisters of the mother are all dark and she knows of no instance of a light colored person in her family. The mother likewise knows many of her husband's family and states that there are first cousins of his who are light and have been "mixed up with the whites" but that these are all the offspring of one uncle and that the light tendency occurs in no other branch. (The information concerning these light negroes furnished in contemptuous tone.)

The hemophilic boy and his 2 brothers are the blackest of negroes and their appearance is certainly against the impression that they may possess white ancestors.

The past medical history states that at birth there was no unusual bleeding from the cord. At the age of 3 or 4, the child began to bleed from the nose once or twice a week. At the age of 6 or 7, it was first noticed that cuts would bleed intermittently for 3 or 4 days. During the 3 or 4 years previous to admission, the family has noted frequent swellings of the ankles, knees and wrists occurring after hard play, usually connected with a fall. These swellings would last a week or more. There was never any hematuria, melena or hematemesis. The boy has never before been hospitalized. He has apparently been normal as to his activities. He had influenza at the age of 1 year, typhoid fever and chicken pox both at 2 years of age. He was a full term baby, born by spontaneous delivery. He sat up at a later date than normal and did not walk for over 1 year. He talked at the "appropriate time." He received no orange juice until the age of 18 months.

He was admitted to this hospital for the first time on May 28, 1935. At this time his chief complaint was bleeding from the gums. He had been bleeding for about 1 week and on the day of admission the bleeding became more profuse and the family became alarmed. The father stated that his diet had been replete with vegetables and that he had had no pain in his arms or legs since the onset of the present bleeding episode. He had been receiving fruit on an average of once a week.

Physical examination revealed an apprehensive, somewhat listless, but coöperative young colored boy, moderately well nourished. He showed marked pallor of the mucous membranes and the conjunctivæ. The eye grounds showed no hemorrhage. The gums, lips and oral mucous membranes were pale; the gums were firm and there was blood oozing from them along all the upper left teeth. The incisors were notched but not of the Hutchinson type. The pharynx was injected and the tonsils were present. The glands showed a generalized enlargement of those of the neck, groin, axillæ and the epitrochlears. The spleen was not palpable. The neck was normal except for the adenitis. The lungs were normal. The heart was rapid (102 per minute). The rhythm was regular; there was no enlargement. There was a systolic murmur heard over the entire precordium. The abdomen was not tender; no palpable organs with the exception of the liver edge which could be felt at the costal margin on deep inspiration. The genitalia were normal. The extremities showed pallor of the nail beds. There was no pain over the long bones and the reflexes were normal throughout.

On June 5, 1935, a tooth was extracted and the patient bled for 3 days, after which he felt well. On June 14, he fell and cut his right little finger. It was noted that he bled readily and soaked the dressings.

Laboratory studies on May 29, 1935, showed the hemoglobin to be 48%; R.B.C. 2,970,000; W.B.C. 7100 of which 55% were neutrophils, 5% eosinophils, 1% basophils and 39% lymphocytes. The blood sugar was 57 mg. %; the blood calcium was 9.8 mg. % and the blood phosphorus 5.2 mg. %. The Wassermann and Kahn tests were both negative. On

June 3, roentgenograms of the knee regions were negative for evidence of scurvy. The boy was discharged on June 14 without definite diagnosis as to the cause of the bleeding.

On July 15, 1935, he returned to the Out Patient Department Dental Clinic where he was not recognized and where the family denied a history of bleeding. Consequently another tooth was extracted. On July 16, he was readmitted to the hospital because of bleeding from the tooth socket. Attempt to control the hemorrhage by thromboplastin and packing locally and 10 cc. of thromboplastin intravenously was unsuccessful. He was still oozing on July 17 when his hemoglobin was 48% and his R.B.C. 2,710,000. His pulse was 130. On July 18 the bleeding continued and an indirect transfusion of 200 cc. of citrated blood was given. One hour after the transfusion there was a chill and a rise in temperature to 104° F. The hemorrhage ceased. Subsequently there occurred a minute amount of hemorrhage for 1 day.

On July 23, he was transferred to the medical service. It was here noted that the mucous membranes, conjunctivæ and nail beds were almost white. The pulse rate was 116, the spleen not palpable. On this day the R.B.C. were 2,300,000 and the platelets 320,000 per c.mm. On August 7, the patient was up and about the ward and a note was made to the effect that he was a disciplinary problem. Four days later it was noticed that there was limping due to considerable swelling of the left knee. This knee was not hot or tender but was painful on motion. On questioning the patient, he revealed that while playing in a wheelchair the night before, he had bumped the knee against one of the arms of the chair. The intern made a diagnosis of hemophilia with hemarthrosis. The bleeding and coagulation times were taken and found to be 2½ minutes and 1 hour and 45 minutes plus, respectively.

Five days later swelling in the knee was subsiding. The patient had some fever which was unexplainable other than by absorption of the products of the clot in the knee joint. On August 21, the knee was flexed to about 120 degrees and there was marked distention of the joint space with little motion possible. The joint was tapped and 20 cc. of bloody fluid obtained. Three days later on repeated tapping, 100 cc. of dark fluid was removed. During this time the patient was receiving daily intramuscular injections of from 10 to 20 cc. of whole blood. On September 1, oozing began from the point at which the needle was introduced for the knee tap 9 days previously. On September 4, he was still bleeding and 10 cc. of fresh rabbit serum was injected intramuscularly. The blood pressure was 108/60, the pulse 180, the coagulation time 38 minutes. The patient was given a transfusion of 200 cc. of citrated blood. For this transfusion both the mother and father were typed and the Wassermann and Kahn tests on both were negative. The following day the pulse dropped to 130, and the coagulation time was 13 minutes. Two days later he was given a third transfusion of 175 cc. of citrated blood. On September 11, rabbit serum was again given intramuscularly. Bleeding continued intermittently from the tap wound from September 1 to 18, 1935.

The boy was kept at rest until October 8 at which time physiotherapy was instituted in an attempt to improve motion in the knee joint. Walking and physiotherapy gave about 30 degrees motion and fair function in the left knee by November 30 when the patient was discharged. During the course of his active bleeding (September 5), the patient complained of abdominal pain beneath the right costal margin. This lasted for but 24 hours and there was no recurrence.

The studies done on the patient during his stay in the hospital included those above recorded and several other coagulation and bleeding times.

In all, there were 12 determinations of the coagulation time. These were as follows:

1935.	Time in minutes.
July 27	19
August 4	5
August 12	105+
August 25	90+
September 4	38
September 6	13
September 11	36
September 18	19
September 20	17
October 1	27
October 2	42
November 4	60+

On February 27, 1936, 5 months after the last bleeding episode had ceased, the coagulation time was 22 minutes. With the exception of the one in which the coagulation time was 5 minutes, the other 12 ranged between 13 minutes and 1 hour and 45 minutes. The bleeding time on all occasions was within the normal limits. The platelet count was normal. The clot retraction was normal on two occasions. On November 4, approximately 7 weeks after cessation of bleeding, the blood was observed not to clot for over 1½ hours, but the retraction was normal when the clot did form. The Wassermann and Kahn tests were negative on 3 occasions. On September 20, 1935, a Roentgen ray study of the left knee was reported as follows: "There is considerable swelling about the left knee joint and the suprapatellar bursa in particular. There is some destruction of the posterior articular surface of the patella with beginning squaring of the intercondylar space" (Figs. A and B). Dr. W. C. Hall, the roentgenologist, was of the opinion that while these findings are not absolutely typical of hemophilia they are undoubtedly due to this condition.^{6,7} On October 9, there was somewhat more bone destruction about this joint, otherwise report was the same as previously noted. On November 6 this knee showed no bony ankylosis. On November 22, the wrists, shoulders, elbows, knees and ankles were examined and, with the exception of one small area on the right knee and the above named changes in the left knee, there was no evidence of bony change.

The boy has continued in good health since the cessation of the bleeding episode in September of 1935. There remains as evidence of his illness only deformity and restriction of motion in the left knee and a prolonged coagulation time.

Summary. A careful review of the literature has failed to reveal a single case of undoubted hemophilia in the negro. The case here reported, excepting for the family history, is typical of hemophilia. In spite of frequent nosebleed in 2 brothers and a maternal uncle and grandfather, the family history cannot be interpreted as the genealogy of a hemophilic. The patient was a very black negro without any ascertainable evidence of white ancestry who presented a history of immoderate hemorrhages from several sources since early childhood. He further showed rapid recovery following hemorrhage and had also the characteristic mischievous temperament which Bulloch and Fildes noted as being so constant that it might be regarded as almost a minor feature of the disease. He developed



A



B

Figs. *A* and *B*.—Roentgen ray picture of the hemarthrotic left knee. *A*, Anteroposterior; *B*, lateral view.



hemarthrosis of the left knee and joint changes typical of those found in hemophilics, though they are not pathognomonic. But 1 of the 13 coagulation time tests was within normal limits. This one was taken during a period of active hemorrhage. The coagulation time was still markedly prolonged 5 months after cessation of hemorrhage. The platelet count, the tourniquet test, the clot retraction, the Wassermann and Kahn tests were all negative.

It is generally recognized that a qualitative defect of the blood platelets interfering with proper coagulation of the blood exists in hemophilia. Studies are being made calculated to prove or to disprove the existence of such a defect in the platelets of this patient.

Conclusions. The case here cited is apparently the first instance of hemophilia in the full blooded negro to be recorded.

I wish to express my appreciation of the advice and criticism given by Dr. David L. Farley during the preparation of the manuscript.

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PERNICIOUS ANEMIA IN THE NEGRO.

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ALTHOUGH anemia in the most bizarre forms develops in the negro, true pernicious anemia is considered to be quite rare, a fact borne out by the paucity of the literature on the subject and by the appearance of reports of small series of cases. Carr¹ reported 6 in 148 cases of pernicious anemia. Willson and Evans² found 8 mulattoes among 111 cases of pernicious anemia in the Johns Hopkins Hospital in 34,280 colored admissions. Eight cases were found by Traut³ in a total of 256 cases of pernicious anemia at Cook County Hospital, where 33% of the admissions were colored. Matthews⁴ encountered 2 instances among 4940 admissions to the

Veterans Bureau Hospital at Tuskegee, Alabama, in 5 years. From among 4503 negro admissions to the Peter Bent Brigham Hospital, Friedländer⁵ reported 3 cases. Jamison⁶ found the records of 12 cases in 121,000 colored admissions to Charity Hospital from 1920 to 1925.

Incidence. The decade 1926 to 1936 was selected because 1926 marks the inaugural of liver therapy in this hospital, the response to which affords an additional diagnostic proof. There were 247,239 colored admissions in this period, of which 43 cases were filed as pernicious anemia. We have rejected 25 of these because of insufficient data, and present below in tabular form 14 cases which we believe to be true pernicious anemia. A brief summary of 4 more presumptive cases, in which the data are too scanty to make them entirely acceptable, are added. The 14 cases represent an incidence of 1 case per 17,659 colored admissions.

In the same period, 277,324 whites were admitted. Of these, 187 cases are listed as pernicious anemia; 98 were taken to be true pernicious anemia and 89 were rejected by the same standards employed in selecting the colored cases. An incidence of 1 white case per 2829 white admissions is obtained, and 1 negro with pernicious anemia to 7 whites. The ratio of white to colored admissions in this period is 1.12:1.

The average age of the negro patients was 52 years, with extremes of 27 and 70 years. Nine of the patients were in the 5th or 6th decade.

Nine of the accepted patients were males, and 5, females. In the white group, the females predominated slightly.

Admissions into the hospital were slightly higher in the spring and summer months; this was also true of the white patients.

The duration of symptoms prior to admission averaged 9 months, with extremes of 2 months and 2 years.

Selection of Cases. All cases selected for this report showed achlorhydria. All had macrocytic hyperchromic anemia of marked degree which responded to liver therapy. They presented one or more of the symptoms of weakness, debility, numbness and paresthesias, breathlessness, palpitation, with or without edema, in the absence of cardiac failure, icterus, and cord changes.

Carcinoma of the stomach, pellagra, sprue, malaria, cirrhosis of the liver, hookworm and fish tapeworm infestation were apparently absent in the cases chosen. Cases having either a history of syphilis or a positive Wassermann were not believed to be acceptable because of the known mimicry of pernicious anemia by syphilis.

Clinical Data. The symptoms exhibited by the accepted cases, with the physical findings, are listed in Table 1.

In all 18 cases of accepted and probable pernicious anemia, the Wassermann test was negative. Further, the spinal fluid Wassermann and cell count were negative in 7; in the remaining cases it was not done.

TABLE 1.—SYMPTOMS AND SIGNS IN 14 CASES.

Symptoms.	No. cases.	Signs.	No. cases.
Weakness	14	Glossitis	9
Dyspnea	10	Icteric sclerae	8
Palpitation	9	Increased knee jerks	8
Paresthesias	9	Cardiac enlargement	5
Edema	8	Systolic murmur	5
Vertigo	7	Loss of vibratory sense	4
Diarrhea	6	Ataxia	3
Anorexia	5	Absent knee jerks	2
Abdominal distress	5	Babinski	2
Sore tongue	5		
Difficulty in walking	2		
Incontinence	2		
Precordial pain	2		

Achlorhydria was present in all cases, usually on more than one examination, and in 5 of the 18 cases, histamine was employed. In addition to the 8 cases showing clinical jaundice, of which 3 showed icterus indexes of 22, 40, and 50, respectively, there were 2 with an icterus index of 8.

For the sake of brevity, the characteristics of the erythrocytes on smear were omitted from the table of accepted cases, and reports of probable cases. All of the smears showed anisocytosis, poikilocytosis, and usually polychromatophilia, stippling and macrocytes. Some showed normoblasts and megaloblasts. Unfortunately, reticulocyte counts were not made frequently enough to make possible the presentation of a curve. However, after institution of liver therapy, for a varying number of days, in 8 of the 14 accepted cases, there were reticulocyte counts indicating bone marrow response. The maximum reticulocyte count available in the 8 cases were 4.5, 5, 6, 9, 9, 12, 17, and 29% respectively. Some of these obviously were not made at the time of the anticipated peak response.

The white counts in all cases but one, which was 6000, were below 4000, practically all of them being between 2000 and 3000. The neutrophil cells were usually from 30 to 40% of the total on admission, and with liver therapy increased to a normal percentage.

In Table 2 are presented data pertinent to the 14 accepted cases. Minimum and maximum erythrocyte counts, expressed in millions, and minimum and maximum hemoglobin values have been arranged for comparison. The total number of red counts done in these cases varied. In one, only 3 were done, in one 5, and 11 in a third. Of the remaining, two had 4 counts, two 6, two 8, two 9, and two 10 counts. Hemoglobin is recorded in grams per cent. In those instances where estimation was done by other than the Newcomer or Sahli method, the value was converted to grams on an arbitrary basis of 16 grams being 100%.

In addition to the 14 cases accepted as definite pernicious anemia, there were 4 in which the evidence available points to the probability of this disease, but in which the insufficient laboratory data do not justify an unqualified diagnosis. These cases are shown on page 755.

TABLE 2.—DATA IN 14 CASES OF PERNICIOUS ANEMIA IN NEGROES.

Case.	Sex.	Age.	R. B. C.		Hb. (gm.).		Color index.		Mean corpuscular volume.		Days before maximum response.	Liver.			Year.
			Min.	Max.	Min.	Max.	Before therapy.	Peak response.	Before therapy.	Peak response.		Oral vials.	Parental, cc.	Transfusion, hospital day.	
1	F.	60	1.44	4.25	6.3	11.6	1.8	0.9	103.6	87.7	34	57	1930
2	F.	67	0.41	1.5	3.2	6.4	2.5	1.3	26	79	..	2	1930
3	F.	27	0.44	2.9	2.4	0.4	1.7	0.7	42	152*	17	1	1930
4	F.	41	1.04	3.2	5.6	7.2	1.6	0.72	21	38	1931
5	M.	43	1.97	3.8	6.4	1.1	100	100	18	56*	10	1932
5a	2.38	4.25	11.2	12.8	1.5	0.9	37	..	29	1935
6	M.	70	1.95	3.01	8.0	10.6	1.0	19	114	1930
7	M.	73	1.5	3.07	4.0	9.5	1.3	0.9	51	85	..	9	1933
8†	M.	41	1.14	3.02	4.8	11.7	1.3	1.2	125	28	..	53	1933
8a	0.61	3.15	2.8	9.6	1.5	0.9	25	..	22	1934
9	M.	43	1.46	3.43	5.6	12.0	1.2	1.0	36	..	43	1935
10	M.	59	0.36	1.54	1.7	1.4	120	10	..	31	1935†
11	M.	57	0.81	2.47	3.6	1.8	130	16	1 and 2	1935
12	M.	56	0.62	3.60	5.3	2.6	51	84	..	7	1935
13	M.	51	1.99	4.2	6.4	11.0	1.0	130	89	30	90	1929
14	F.	41	1.07	3.9	4.8	13.6	1.4	1.0	62	..	92	1933
14a	2.86	4.0	8.0	1.8	59	110	31	1935§

* Venticulin.

† Followed weekly to July, 1936. 1 cc. intramuscularly weekly.

‡ Died of pneumonia.

§ Had taken 2 drams of liver extract daily. In 1934, red blood count was 4.10; hemoglobin 13.6.

Case Reports. CASE 1.—I. H., male, aged 24, complained of abdominal pains, dyspnea, weakness, palpitation and diarrhea. Examination showed a glossitis, icteric scleræ, and absence of knee jerks. Red blood cells numbered 580,000, hemoglobin 2.2 gm., hematocrit 6.5%, mean corpuscular volume 112 cu. micra. The smear presented normoblasts, megaloblasts and 4.5 reticulocytes. Icterus index was 50. One transfusion was given. Patient developed pneumonia and died before further studies could be made.

CASE 2.—T. G., male, aged 59, presented symptoms of sore tongue, vertigo, diarrhea, paresthesias, and inability to walk. On examination, there were glossitis, icterus, absence of vibratory sense, and spasticity of the lower extremities. Spinal fluid was negative. Red count was 1,790,000, hemoglobin 8.41 gm., color index 2.3, cell volume 108. Icterus index was 40. Clinical improvement took place in 17 days after one transfusion and 17 vials of liver extract. Red count increased to 2,630,000, with color index of 1.1. Necropsy showed enlarged, gray spleen and the liver contained some hemosiderin.

CASE 3.—P. Y., male, aged 51, complained of inability to walk. Examination showed hypoactive reflexes. The red blood cells were 1,790,000, macrocytes were present on smear. After 210 vials of liver extract in 97 days, the red count mounted to 4,500,000.

CASE 4.—O. H., female, aged 43, presented weakness, dyspnea, edema and difficulty in walking, with numbness of the feet. Examination showed hyperactive reflexes and positive Romberg. There were 670,000 red blood cells, with mean corpuscular volume of 112 cu. micra. After 5 days of liver, the reticulocytes were 13%. At the end of 3 weeks of liver therapy, the red count had risen to 1,780,000.

Discussion. An incidence of 1 colored to 7 white patients with pernicious anemia, on a basis of equally rigid selection, is not so great a difference between the two races as has been generally taught in the past. There may be two possible explanatory factors. It is conceded, by physicians who have had experience in both the Mid-west and the South, that pernicious anemia is less common here than in the former area. Second, due to the large percentage of negro admissions at Charity Hospital (45%), probably a larger number of this race is available for comparative study than in any other institution admitting both colored and white patients.

It is felt that a selection on the basis outlined above is sufficiently rigid to warrant acceptance of these cases as true Addisonian anemia. In the 14, there occurred a macrocytic anemia with high color index and achlorhydria, and response to liver extract, in the absence of other conditions simulating the picture of pernicious anemia. It is admitted that the blood picture in each case should have been followed to normal levels, and also that in some, the liver therapy was inadequate. However, this could not be avoided because deplorable overcrowding makes prolonged hospitalization impossible. Too, the negro is very prone to desert when he feels subjectively improved.

Four of the 14 cases chosen have been studied personally by us, and we have followed one through a relapse while he was unable, for financial reasons, to procure liver. On the initial admission his extreme ataxia compelled him to be carried to the hospital. He now walks unaided to the hospital each week to receive an injection of liver extract.

Striking is the frequency of cord changes as manifested by subjective complaints of numbness, ataxia, walking difficulties, and the finding of abnormal reflexes, and loss of vibratory sense. These occurred in a higher percentage of cases in this series than would be seen in white patients. This is readily explained by the fact that, generally speaking, the pathology of disease is more advanced in the negro, on admission, than in the white.

It is universally accepted that pernicious anemia, rarely, if ever, occurs in the full-blooded negro. This is probably true. Of our series, we know definitely that the 4 we observed were of mixed white and negro blood, and it is quite possible that the rest were also.

Summary. 1. Fourteen acceptable and 4 presumptive cases of pernicious anemia have been found in almost a quarter million negro admissions to Charity Hospital.

2. The low incidence of pernicious anemia in the white admissions to this hospital gives a ratio of 1 colored to 7 white patients with this disease.

3. The symptoms of the negro are almost the same as of the white patients, differing only in degree, due to the notorious self-neglect of the former race.

4. Pernicious anemia probably does not occur in the pure blooded negro, though in only 4 of our cases has a mixed ancestry been established.

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ADDISON'S DISEASE IN THE NEGRO.

REPORT OF SEVEN CASES.

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OVER 300 cases of Addison's disease are reported annually in the registration area of the United States.¹ It is generally accepted that the disease is prone to occur more frequently in members of the

laboring class. At necropsy, tuberculosis has been the etiologic factor in the great majority of cases.² Considering the relatively high incidence of tuberculosis among Negroes, and the heavy manual labor by which many of them earn their livelihood, it is surprising that only 7 cases³ of this syndrome in the colored race appear to have been reported. A casual inquiry at a few neighboring hospitals has brought to light 6 previously unreported cases which we are privileged to add to the 1 recently observed at the University Hospital. This would seem to indicate that this clinical picture is more frequent among Negroes than is generally appreciated.

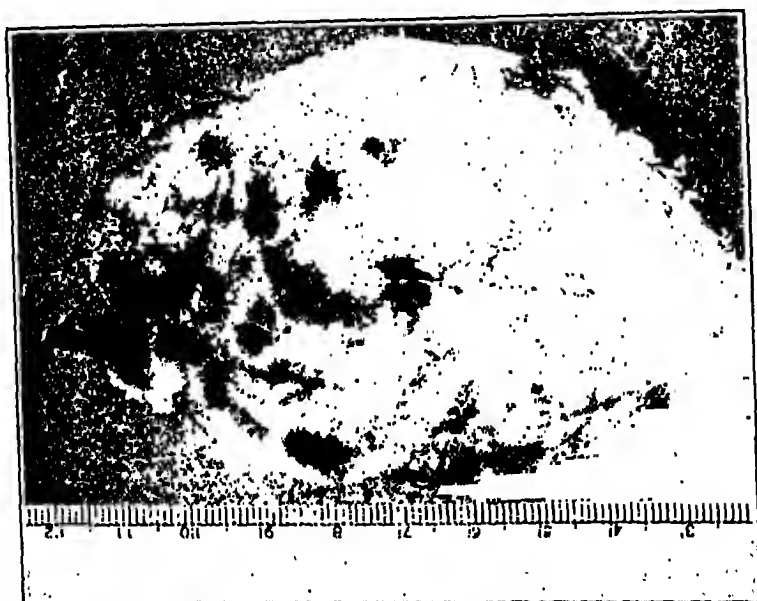


FIG. 1.—Case 1. Intense cutaneous pigmentation.

Case Abstracts. CASE 1.—(University Hosp. No. 35-21267). A 60-year-old ebon Negress was admitted to the service of Dr. Alfred Stengel in an extremely weakened condition, the increasing pigmentation of the skin having been noted for 7 months. Her husband insisted that she had previously been a "high-yellow" Negress. For 2 months she had frequently vomited, lost 23% of her body weight, and become increasingly fatigued, necessitating bed confinement at home under her physician's care 3 weeks before hospitalization.

Upon admission, physical examination revealed an extremely weak, intensely pigmented, elderly Negress, temperature 98.2°, pulse 84, respiration 34, several pigmented naevi of the face, general loss of muscle tone, diffuse faint striæ of the skin, patchy buccal and lingual pigmentation, hypotension (65/45), and fine moist râles at the apex of the left lung. Urinalysis, blood count, Wassermann test, urea nitrogen and sugar determinations were not abnormal. The blood sodium (130.7 m.eq./L.) and chloride (89.4 m.eq./L) were diminished. No acid fast bacilli were found in a single sputum examination. A tentative diagnosis of Addison's disease with active pulmonary tuberculosis was made, and large doses of potent adrenal cortex extract and sodium chloride were administered. The patient gradually lapsed into coma, with steadily falling blood pressure and terminal hyperpyrexia (106°), death supervening 41 hours after admission to the ward.

AUTOPSY: the adrenals were replaced by fibrocaceous tuberculous masses, accompanied by mesenteric tuberculous lymphadenitis and bilateral apical fibrous tuberculosis. An atrophic thymus persisted. The previously mentioned pigmentation of the skin and mucosal surfaces was also faintly visible in the urinary bladder.



FIG. 2.—Case 1. The tongue, showing patchy pigmentation.

CASE 2.—(Presbyterian Hosp., New York). A 54-year-old Negress was admitted complaining of weakness, loss of weight, and increasing skin pigmentation for 4 months. At postmortem examination bilateral adrenal tuberculosis, obsolete pulmonary tuberculosis, and miliary tuberculosis were demonstrated.

CASE 3.—(Presbyterian Hosp., New York). A 33-year-old Negro returned to the hospital 3 years after removal of a tuberculous kidney, having noticed skin pigmentation for 1 year. Three weeks before admission he ceased work because of rapidly developing weakness, anorexia and vomiting. At autopsy there were found obsolete pulmonary tuberculosis, bilateral adrenal tuberculosis, tuberculous pneumonia and peritonitis.

CASE 4.—(Presbyterian Hosp., New York). A 39-year-old Negro came to the hospital stating that he had "grown three shades darker in the past year," and had become quite weak during the previous 6 weeks. Tuberculosis was clinically evident in the left kidney, the seminal vesicles and the right epididymus. Developing severe adrenal insufficiency, the patient was successfully treated with sodium chloride and discharged. Seven months later he died suddenly, presumably due to hypoglycemia which he had exhibited previously, but an autopsy was not performed.

CASE 5.—(Bryn Mawr Hosp., No. 019754). A 65-year-old Negro was admitted to the service of Dr. J. L. Spangler with active pulmonary and epididymal tuberculosis, first recognized 3 months previously. The chief complaint was the nightly occurrence of brief clonic spasms of the leg muscles, with general soreness and weakness necessitating confinement in bed for a fortnight. Increasing pigmentation of the skin for several months was affirmed by the patient's pastor. Asthenia, emaciation and hypotension (85/58) were the paramount physical findings, while during the 3 weeks before death there appeared anorexia, vomiting, hiccoughs, incoherence and hypomania. At autopsy the adrenals were found to be entirely destroyed by caseous tuberculosis, with less extensive lesions of the lungs and genital tract.

CASE 6.—(Philadelphia General Hosp., Autopsy No. 21967). A 26-year-old Negress was admitted to the service of Dr. H. D. Jump in hypoglycemic coma, with history of general malaise, weakness, loss of weight and skin pigmentation for 1 year. Glucose therapy failed to alleviate the semistuporous state of the patient, and she died 6 days later. Fibrocaseous tuberculosis of both adrenals was found at autopsy.

CASE 7.—(Philadelphia General Hosp., Autopsy No. 29416). A 21-year-old Negro, with old Pott's thoracic deformity and history of previous hypoglycemic coma, was admitted to the service of Dr. W. E. Robertson with severe abdominal pain and vomiting, the second exacerbation of these symptoms. He presented hypotension (80/40), pigmentation of the mouth and hands, and slightly subnormal blood chloride level. He died 3 days later of acute adrenal insufficiency. At autopsy no pulmonary tuberculosis could be demonstrated, but the vertebræ and both adrenals were extensively involved.

Discussion. The comparison of the 14 reported cases of Addison's disease in the Negro present many interesting conclusions. Eight of the patients were malés, 6 were females, and with one possible exception (Case 4), all died with signs of adrenal insufficiency. Their ages ranged from 21 to 65 years, the average being 44 years at death. Increasing skin pigmentation in 12 of the 14 cases had been recognized by the patients or their friends for several months before hospitalization. Anorexia, vomiting, loss of weight and increasing weakness were prominent features of almost every history. Hypotension was pronounced in each case where blood pressure readings are given. The maximum duration of life after recognition of the disease was 7 months, while 6 of the victims succumbed within 8 days after hospitalization. Tuberculosis was the etiologic agent in each of the 11 cases which came to autopsy, 1 case (that of King and Mulholland) also showing a congenital absence of one adrenal.

Summary. 1. Seven cases of Addison's disease among Negroes are presented, bringing the total number in the literature to 14.

2. The occurrence of this syndrome in the Negro would seem to be much more frequent than the recorded cases would indicate.

3. The diagnoses as a rule were made in the late or terminal stages, but otherwise the symptomatology differed in no way from that usually seen in white patients with this syndrome.

4. Tuberculosis was the etiologic agent in each of the 11 cases which came to autopsy.

We wish to express our appreciation for the privilege of presenting these additional cases to Dr. Robert Loeb (Cases 2, 3 and 4), to Dr. John L. Spangler (Case 5), and to Drs. Jump, Robertson and Welty (Cases 6 and 7). The last 2 cases are presented in more detail from the standpoint of hypoglycemia by Dr. John Welty in the following article.

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HYPOGLYCEMIA IN ADDISON'S DISEASE.

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THE occurrence of hypoglycemia in affections of the adrenal glands has been noted both clinically and experimentally by many observers; current textbooks, however, fail to mention it. Bierry and Malloizel,¹ in 1908, noted reduction of blood sugar values in dogs following adrenalectomy; Borges² confirmed this observation 2 years later and in addition reported 3 cases of Addison's disease, all of which presented low blood sugar levels. Janney and Isaacson,³ in 1918, stated that hypoglycemia frequently resulted from hypoadrenal function, showing experimentally that it developed regularly after thyroidectomy and calling attention to its frequent occurrence in destructive lesions of the adrenal glands. In an extensive review of Addison's disease in 1925, Rowntree⁴ noted the very frequent finding of a fasting blood sugar below the normal level and stated that in 2 of his cases it had reached the low figure of 45 mg. %. Chapman⁵ reported a case in 1926 which presented a flat glucose tolerance curve and Wadi⁶ later called attention to the similarity of symptoms in Addison's disease and hypoglycemia, describing at that time a case of the former with convulsions relieved by dextrose administration; diagnosis in this case was proved by necropsy. Turner⁷ and Porges and Adlersberg⁸ also reported cases showing marked increase in the carbohydrate tolerance. Waitchope's⁹ recent review of hypoglycemia summarizes the knowledge to date upon this subject.

A few observers have disagreed with these findings. Sakaguchi¹⁰ noted no definite hypoglycemia in 5 cases of Addison's disease and later was unable to produce this phenomenon by removal of the adrenal glands in rabbits. He concluded that adrenalectomy has no great influence upon the sugar assimilating power of the organ-

ism. Rosenow and Jaguttis¹¹ believed, after study of a patient and a critical survey of previously reported cases, that hypoglycemia was not a constant symptom of Addison's disease; these workers, however, noted the paradoxical hyperglycemia following adrenalin administration which was later observed by Turner.⁷

The following proven cases of Addison's disease are reported because they showed evidence of marked hypoglycemia with coma relieved by dextrose administration, and because in one case symptoms of the increased sugar tolerance overshadowed those of the destructive adrenal lesion and made the differential diagnosis very difficult.

Case Reports.—CASE 1. J. A., a 21-year-old, American born Negro, was admitted to this hospital (service of Dr. W. E. Robertson), on February 18, 1935, complaining of abdominal pain and vomiting for 3 days. The history of his present illness dated back to early December, 1934; following a "cold" of 2 days' duration manifested by cough, headache, and vomiting, the patient rather suddenly went into deep coma. A hospital examination of the blood revealed the glucose level to be 40 mg. % with a carbon dioxide combining power of 30. He was given 100 cc. of 50% glucose in normal saline solution by intravenous injection at once; during this procedure the patient regained consciousness rather dramatically and talked rationally. He remained in the hospital 14 days, during the first 2 of which a mild fever and cough were present. He was discharged in apparently good condition with the final diagnosis of hypoglycemia and acute bronchitis. It was believed that the former was incidental and precipitated by starvation during the upper respiratory infection. No additional studies were done. Following discharge he remained well until 11 days before admission at which time he vomited without apparent reason after a breakfast of hominy grits. Following this there were no symptoms until 3 days before admission when, in the midst of a breakfast of oatmeal, he suddenly and without warning vomited. While vomiting he felt sharp pain in the midepigastrium which did not radiate and which disappeared within a few minutes. The same course of events occurred several times during the next few days. Dull, frontal headache accompanied the gastro-intestinal upset.

The family history was negative. Review of the past history revealed that he had been "hunchbacked" since the age of 4. He did not believe that there had been any change in the color of his skin which he stated had always been very black. He had had rare heterosexual experiences. Abdominal upsets with vomiting had been noted frequently for several years.

Physical examination revealed a small, kyphotic Negro with a peculiar "mouthy" speech, lying in bed in no apparent pain or distress. Mentally he was clear, alert and cooperative but of low intelligence, answering question in monosyllables. The skull was small, long and symmetrical, the jaw markedly prognathous. Prominent lips protruded beyond the very flat nose. The skin was extremely black. Examination of the eyes revealed nothing externally but the fundi presented bilateral temporal pallor. The teeth were dirty, poorly developed and thin with very pointed canines. The tongue was pale pink with irregular patches of black pigmentation; similar areas were present on the buccal mucosa and palate. Examination of the back showed an extreme dorsal kyphosis and lumbar lordosis, the spine being practically doubled upon itself. The chest was deep and deformed and the lower ribs rested on the pelvic brim. The heart and lungs seemed normal. The blood pressure was 95 systolic and 75 diastolic bilaterally. Slight midabdominal tenderness was noted. The external genitals

were normal. The narrow, short hands were in marked contrast to the long tapering fingers. Palms, soles and nail beds were extremely black.

Urinalyses, urea clearance tests and phénosulphonphthalein tests were negative as was the blood Kahn reaction. Erythrocytes varied from 3.8 to 4.1 million. The leukocyte count averaged 15,000 (lymphocytes 60% or more). Blood plasma chlorides fluctuated between 550 and 580 mg. % (as sodium chloride). Blood calcium and phosphorous levels were normal. Blood urea nitrogen varied from 25 to 35 mg. %.

Blood sugar examination on admission showed a fasting level of 68 mg. % (reducing power of tungstic acid filtrate determined by the Folin-Wu method). A number of glucose-tolerance tests were done, all of which showed a practically flat curve. A representative 3-hour curve after 1½ gm. of glucose per kg. administered to the fasting patient by mouth was:

Fasting . . .	75 mg. %	2 hours . . .	75 mg. %
30 minutes . .	72 mg. %	3 hours . . .	72 mg. %
1 hour . . .	72 mg. %		

A typical 6-hour curve under the same conditions was:

Fasting . . .	72 mg. %	3 hours . . .	70 mg. %
30 minutes . .	77 mg. %	4 hours . . .	63 mg. %
1 hour . . .	80 mg. %	5 hours . . .	59 mg. %
2 hours . . .	80 mg. %	6 hours . . .	58 mg. %

Roentgen-ray examination of the skull was negative. There was no Roentgen evidence of adrenal calcification. Chest films showed nothing suggestive of pulmonary tuberculosis. The basal metabolic rate, carefully corrected for the patient's deformity, was -19. Other laboratory studies were essentially negative.

Following the first few days on the ward the patient was in good condition, ambulatory, and was kept in the hospital solely for the purpose of further studies. The systolic blood pressure varied from 80 to 90 and the diastolic from 50 to 60. A tentative but questioned diagnosis of Addison's disease was made. A salt-free diet for the purpose of proving this was considered but not instituted because cortical extract could not be obtained for use in a possible crisis. The patient was discharged April 10, 1935.

He continued to feel well until May 5, 1935, when there was recurrence of the vomiting and transient abdominal pain. Three days later he returned to the hospital where examination was as before. Admission blood sugar was 77 mg. %. Blood pressure was 90/60. On May 10, the patient rather suddenly went into profound shock with a cold clammy skin, subnormal temperature and a cardiac rate at the apex of 30 beats per minute. Soon he was in deep coma and the corneal reflex was unobtainable. Intravenous administration of 1000 cc. of 10% glucose in normal saline was begun; he reacted almost at once and within 30 minutes was fully conscious. Eighteen hours later, during which time cortical hormone had been obtained and administered together with glucose and saline, shock was again prominent. The patient failed to respond and died within the hour.

Necropsy (Dr. R. P. Custer) revealed bilateral fibrocaceous tuberculosis of the adrenal glands. Histologically, there were a few very small islands of cortical and medullary tissue remaining. So-called "status thymico-lymphaticus" was also noted with marked hypoplasia of the heart, aorta, and peripheral arteries. There was a healed primary tuberculous pulmonary complex. The right renal lymph nodes presented active fibrocaceous tuberculous lymphadenitis. A healed Pott's disease was present involving the upper thoracic region.

CASE 2.—V. M., a 26-year-old, American born Negress, was admitted to this hospital (service of Dr. H. D. Jump), on June 16, 1930, in a state of semicoma. According to the history obtained from relatives she had been

complaining of weakness, weight loss and malaise during the preceding year. A perverted appetite for sweets had been prominent and shortly before admission she had consulted a physician. He had told her that the diet contained too much carbohydrate food and advised one consisting chiefly of vegetables which the patient followed rather faithfully. It had also been noted that the color of the skin had been getting darker for the past year, it now being dark shiny black whereas it had originally been light brown. Aside from these symptoms the patient had been well until the day of admission when she was found by a member of her family in an unconscious state.

Examination revealed a confused, negativistic, semicomatose colored female. The skin was ebony black and glistening with the nail beds deeply pigmented. The mouth was badly infected but no pigment deposits were seen. There were palpable cervical lymph nodes. The pupils were dilated but reacted promptly to light. Examination of the lungs and heart presented nothing unusual. Blood pressure was 90/60. The admission blood sugar was 50 mg. % with a carbon dioxide combining power of 43. Other laboratory studies were essentially negative. Following intravenous glucose the patient responded and improved temporarily. However, she later became apprehensive and semistuporous; death occurred 6 days after admission.

Necropsy (Dr. J. O. Collins) revealed bilateral fibrocaceous tuberculosis of the adrenal glands and findings suggestive of "status thymico-lymphaticus." The pathologist stated that practically all the adrenal cortex, bilaterally, was destroyed but did not comment upon the amount of adrenal medullary tissue present.

Discussion. In these 2 cases of Addison's disease hypoglycemia was the outstanding manifestation causing coma subsequently relieved by dextrose administration. Case 1 was a particularly difficult diagnostic problem; it was seen by a number of competent endocrinologists none of whom could definitely decide whether the pathologic lesion was in the adrenal gland, the pituitary gland or the pancreas. The relatively normal serum chloride in Case 1 deserves comment. It is well known that patients with destructive adrenal lesion and adrenalectomized animals respond dramatically to sodium chloride. However, such individuals show low blood chlorides. In this case the normal serum chloride level strengthens the belief that the glucose was specific.

Turner⁷ attributes hypoglycemia in Addison's disease to destruction of the adrenal medulla; the fact that adrenalin administration with glucose causes hyperglycemia lasting several hours favors this theory. In normal individuals there is a delicate balance between insulin secretion which lowers blood sugar and adrenalin secretion which raises blood sugar. This balance is destroyed in lesions of the adrenal medulla, resulting in hypoglycemia. Whether or not this occurs in Addison's disease probably depends primarily on the amount of functioning adrenal medulla present. Such a view explains why all cases do not present this finding.

We believe that with the symptom of hypoglycemia present Addison's disease should always be considered in the differential diagnosis. Hyperinsulinism and Simmonds' disease are perhaps the two affections most difficult to rule out. The former can frequently be differentiated by the absence of the typical symptoms

of pigmentation and hypotension. In addition, the glucose tolerance curve of the two diseases differ rather characteristically. The 6-hour curve of typical hyperinsulinism tends to become progressively lower and shock is usually observed before completion of the test; the curve of Addison's disease is relatively flat, does not decrease sharply and shock is rare unless there are complicating factors such as intercurrent infection or starvation which may deplete the body glucose supply. The glucose tolerance curve of Simmonds' disease resembles somewhat that of Addison's disease. However, extreme cachexia, loss of sexual function, marked depression of the basal metabolic rate (with hypothermia and hypotension), together with loss of teeth and hair (axillary and pubic) are usually present, thus aiding in differentiation.

Summary. 1. Two cases of Addison's disease with hypoglycemic coma as a prominent manifestation are reported.

2. Hypoglycemia in Addison's disease strongly suggests involvement of the adrenal medulla.

3. The characteristic difference in the glucose tolerance curves of hyperinsulinism and Addison's disease is shown.

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OBSERVATIONS ON THE EFFECTIVENESS OF PROTAMINE INSULIN.

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DURING recent months several papers on the use of protamine insulin have appeared in addition to Krarup's monograph from the

Steno Memorial Hospital.¹⁻⁷ Up to this time the following observations have been made about protamine insulin: (1) It acts more slowly than regular insulin, so that if given shortly before a meal the blood sugar will be found to rise considerably after the meal prior to the insulin becoming effective. (2) It acts for a much longer time, so that as long as 24 hours after the injection of this insulin the blood sugar may be normal or even below normal, thus preventing any early morning rise of the blood sugar so often necessitating a midnight dose of the regular insulin. (3) Possibly on account of its slow action, it is accompanied by fewer hypoglycemic reactions, and in most cases it affords a longer period of warning before the more severe symptoms become evident. (4) It steadies the blood sugar level, so that there is less variation from hour to hour than with the regular insulin. (5) It shows its full effect only after from 3 to 5 days from the time of the first injection, so that when protamine insulin is first used, hyperglycemia and glycosuria may ensue for several days. From the last observation it is clear that increases in dosage should be made at well-spaced intervals.

Up to the present, protamine insulin has been given in four ways: (1) To those patients requiring not over 40 units daily, one dose before breakfast has usually been sufficient for the entire 24 hours. (2) In those patients requiring a larger amount, protamine insulin has been given twice daily. (3) In the evening only with regular insulin before breakfast. (4) In the morning before breakfast with a dose of regular insulin administered at the same time. The exact times at which these injections have been given have varied depending upon the distribution of food and exercise during the day. The protamine insulin, whether given in the morning or in the evening, has prevented the early morning rise in blood sugar even in those patients requiring the largest amount of insulin.

PRESENT STUDY. Our experience with protamine insulin extends over a period of 8 months, with a total of 45 patients studied. Our results have, in general, been similar to those already reported.

Patients on Large Doses of Insulin. The earliest patients in whom we used protamine insulin were those who required from 60 to 90 units of insulin daily, and who were so unstable that it was quite impossible to maintain them on the old insulin without frequent hyperglycemia or hypoglycemia. These patients had been taking insulin before breakfast, before supper and at midnight. The protamine insulin was first given 2 hours before breakfast and 2 hours before supper. In no case were the amounts of protein, fat or carbohydrate in the diets altered during the period of standardization with protamine insulin.

In Fig. 1 is shown the effect on blood sugar of protamine insulin as compared with that of regular insulin in a patient in this group. It is evident that there is much less variation in the blood sugar level throughout the 24 hours and that the early morning hyper-

glycemia is entirely prevented. All the patients reported a definite subjective improvement. This consisted in an increase in strength and alertness, with a desire for increased activity.

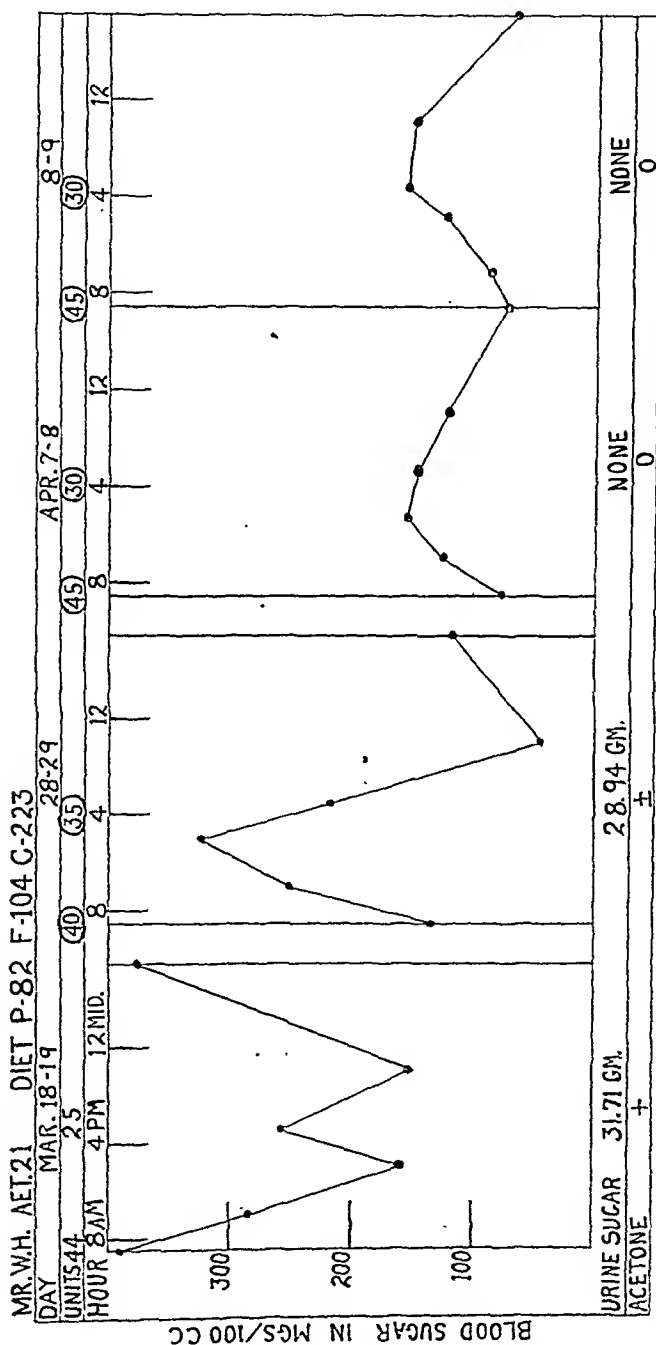


Fig. 1.—The 24-hour blood glucose curves in a severe diabetic on regular and protamine insulin. In the left-hand curve note the heavy glycosuria and wide fluctuations of blood glucose in contrast to the absence of hyperglycemia and glycosuria with protamine insulin. This patient has purposely been kept on a high carbohydrate diet because of previous malnutrition and a marked lipemia. Numerous within circles indicate protamine insulin. Acetone is recorded qualitatively in the 24-hour specimen. Venous blood for sugar determinations was taken at 7 and 10 A.M. and 2, 5 and 10 P.M. *P, F, C* indicate the daily allowance in grams of protein, fat and carbohydrate, respectively.

The hyperglycemia and glycosuria which have been reported as following the first use of protamine insulin have been present in several of our patients, but was marked in only one. This patient was a young woman of 22, slightly overweight, with diabetes of 15 years' duration, taking from 80 to 90 units of insulin per day. There was an increase in her blood sugar to 480 mg. per 100 cc. of blood and an excretion of 155 gm. of glucose on the fourth day of protamine insulin, on a diet of 167 gm. of available glucose. The urine also contained a considerable amount of acetone and acetoacetic acid. It seemed necessary to give her regular insulin in the morning and protamine insulin in the evening, and on this combination she was maintained satisfactorily.

Without exception the early morning blood sugar rise, even in those patients requiring large amounts of insulin, has been prevented. In only 3 of our patients have we felt that it was more satisfactory to give regular insulin in the morning and protamine insulin in the evening. In 3 patients protamine insulin was discontinued altogether, in 1 because of a severe reaction which accompanied overexertion and overindulgence in alcohol, and in 2 because of lack of coöperation.

During the period of regulation on protamine insulin, when there was hyperglycemia and glycosuria a moderate amount of acetone was present in the urine. However, after adjustment, we have found acetone only occasionally, as in the case of patients on regular insulin.

Aspects of Replacement. The amount of protamine insulin necessary to replace regular insulin has been found by us to vary considerably. Patients who required over 50 units of regular insulin daily have required practically an equal amount of protamine insulin to replace it. On the other hand, patients taking from 15 to 50 units daily have required definitely less of the protamine insulin. The average daily amount of regular insulin taken by all the patients studied was 37 units, while the average amount of protamine insulin necessary to replace this was 30 units. The average number of injections daily was reduced from 2.3 to 1.4.

In patients using 2 doses of protamine insulin various attempts have been made to distribute it throughout the 24 hours, so that there would be the least possible interference with their daily lives. While the régime was not satisfactory in all cases, in some we found that if five-sixths of the daily amount of protamine insulin were given 1 hour before breakfast and one-sixth at 7.30 P.M., a satisfactory balance was obtained. The morning dose was available for the lunch and supper, while the evening dose maintained the patient during the night and through breakfast. This obviated the necessity of arising 2 hours before breakfast and of taking a dose of insulin in the middle of the afternoon.

Transfer to Protamine Insulin Without Hospitalization. Our experience with the hospitalized patients was such that we felt that those in the out-patient clinic already adjusted on 2 doses of regular insulin daily could be transferred successfully to 1 dose of protamine insulin without the necessity of entering the ward. We have made this change in over 30 patients. It was possible to do this by giving an amount of protamine insulin 1 hour before breakfast equal to the morning dose of regular insulin, at the same time omitting the evening dose. After several days some of the patients have required an increase in this dose, though in none of the group

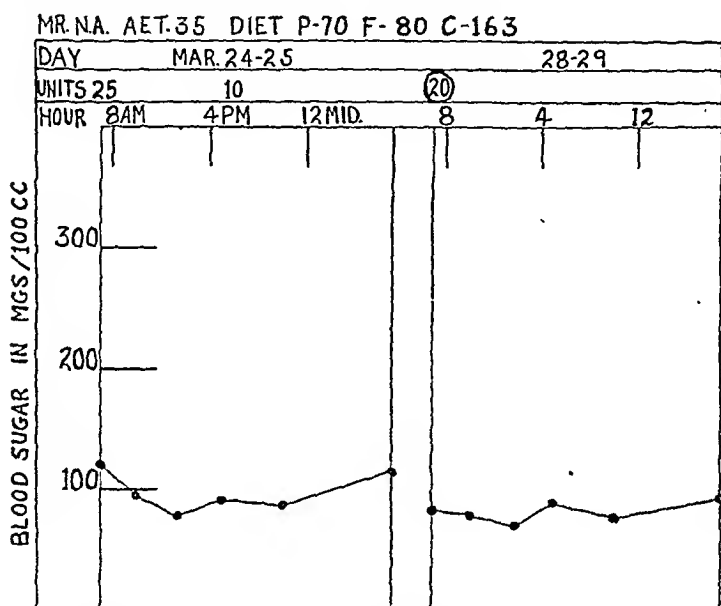


FIG. 2.—The effectiveness of one dose of protamine insulin in a moderately severe diabetic, previously controlled with 2 doses of regular insulin. Note the decrease in units required. Venous blood for sugar determinations was taken at 7 and 10 A.M., and 2, 5 and 10 P.M. P, F, C indicate the daily allowance in grams of protein, fat and carbohydrate, respectively.

has it been necessary to give an amount of protamine insulin equal to the total of the 2 doses of regular insulin formerly given. On account of the slow action of protamine insulin we have found that if 20% of the total daily carbohydrate is given at breakfast and 40% at each of the other meals, a better balance can often be maintained. Small supplementary feedings during the morning, afternoon and evening are sometimes an aid in affecting this.

Only occasional slight hypoglycemic reactions, and no other untoward incidents of any sort have occurred in this group of patients. Furthermore, every patient in this group has felt better on the protamine insulin. We have not yet given protamine

insulin without hospitalization to patients taking over 40 units of regular insulin daily.

In Fig. 2 are shown the blood sugar determinations before and after a change from 2 doses of regular insulin to 1 dose of protamine insulin daily.

It is possible with care to adjust on protamine insulin patients in the clinic who have not had previous experience in controlling their diabetes. When such patients cannot be hospitalized they can be given a larger dose of protamine insulin than of old insulin without fear of reaction. Our experience with this type of case has been limited, but satisfactory.

Hypoglycemic Reactions. Hypoglycemic reactions have been reduced both in number and in severity. They have occurred mostly in patients taking large doses. On all occasions except one, they have reacted promptly to sugar in the form of glucose or orange juice. A man, aged 29, taking 85 units of protamine insulin daily, had a severe reaction in the early morning following an evening of dancing and of somewhat excessive use of alcohol. This reaction will be reported in detail at a later time. On the day before his severe reaction he had stated in clinic that he had never felt so well during the 12 years of his diabetes, nor had he had so few reactions as in the previous weeks while using protamine insulin. Attention may be called to the fact that he had been very unstable on regular insulin.

As has been noted by others, we have found that hypoglycemic reactions following protamine insulin may occur at any time up to 24 hours after the latest preceding dose. They are sometimes only temporarily relieved by sugar, recurring in 1 to 2 hours and requiring further sugar for their control.

Comparison of Effect of Regular Insulin and Protamine Insulin on Blood Sugar. To determine the interval of time between the injection of protamine insulin and its first effect on the blood sugar as compared with the regular insulin, 12 patients were studied. These patients having had no food or insulin since the preceding day were given regular insulin and protamine insulin on succeeding days. Seven blood sugar determinations by Benedict's method were done at 15-minute intervals on arterial blood from finger prick. The insulin was given immediately after the first specimen of blood had been taken, so that 1 determination was done before and 6 after the insulin was administered. Equal doses of regular insulin and protamine insulin were given to each patient. These approximated the regular morning dose of insulin and varied from 10 to 40 units. On 1 patient the examinations were repeated with 10 units on each of the first 2, and 30 units on each of the second 2 examinations, so that in all there were 26 tests on the 12 patients.

The results of these examinations were studied in order to determine (1) the duration of time between the insulin injection and the

beginning of the consequent fall in the blood sugar, and (2) the amount of the fall in blood sugar which occurred in the 90 minutes during which blood sugar determinations were done. In Table 1

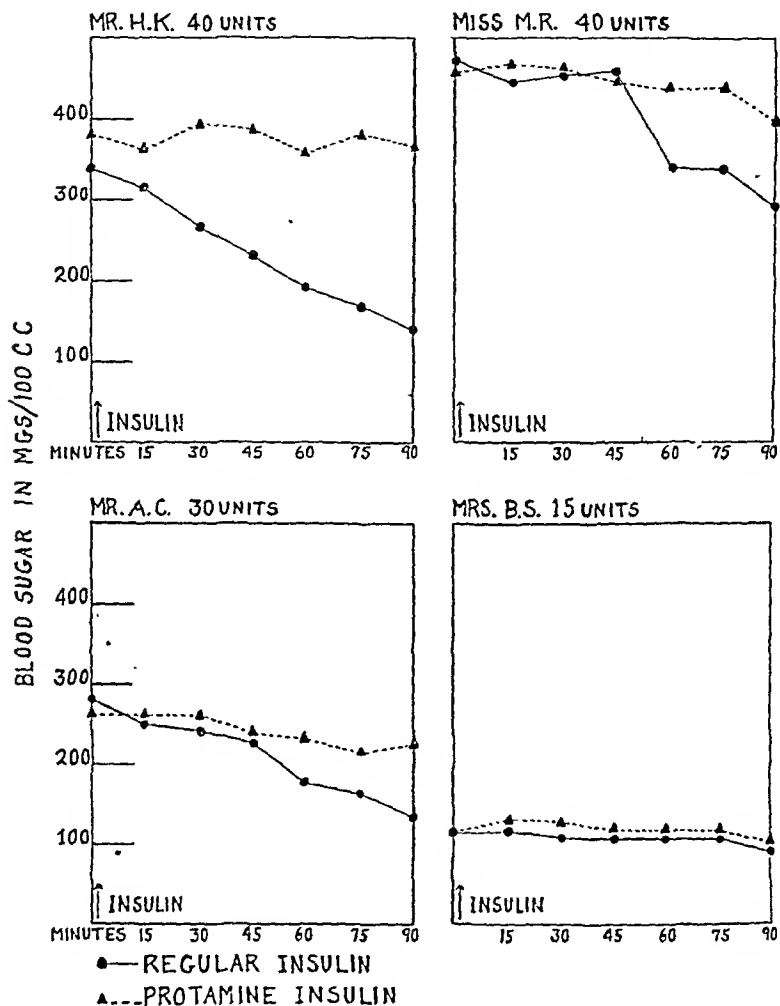


FIG. 3.—Comparison of the rapidity of action after subcutaneous administration of regular insulin and protamine insulin on successive days. The same dosage was used with both, and the amount coincides with the dose of regular insulin previously used before breakfast. Arrows indicate the injection of insulin after the fasting level had been obtained. Note the sharp drop after regular insulin in Mr. H. K., and the delay of 45 minutes in Miss M. R. In both instances no appreciable effect from protamine insulin was evident until 90 minutes had elapsed. The failure of Mrs. B. S. to respond is probably a reflection of the normal fasting level.

is shown the elapsed time between the injection of insulin and the first definite fall in blood sugar.

It is quite evident that the regular insulin acts more rapidly.

In 7 examinations with regular insulin the first definite decrease in blood sugar occurred at the end of 15 minutes after the insulin was injected, while following protamine insulin, only 2 showed any effect in 15 minutes and 10 showed the first effect in from 30 to 60 minutes. In Fig. 3 are shown the blood sugar curves on regular insulin and on protamine insulin in 4 patients who received from 15 to 40 units. One patient did not react until 90 minutes after receiving protamine insulin. The patient on whom the test was repeated with larger doses of insulin showed the first effect with 10 units of regular insulin in 30 minutes and with 10 units of protamine insulin in 60 minutes. When the test was repeated with 30 units the effect was evident in 15 and 45 minutes respectively. In only 1 patient did the protamine insulin react more rapidly than the regular insulin. It is evident, therefore, that while protamine insulin is slower acting than the regular insulin, there is much variation in the time at which each shows a definite effect on the blood sugar.

The average total decrease in blood sugar during the 90-minute period following the injection of regular insulin was 99 mg. per 100 cc., or 36% of the original fasting blood sugar. After protamine insulin the average fall in blood sugar was 28 mg. per 100 cc., or 12%. It would appear that, in accord with clinical observations, the action of the protamine insulin is definitely postponed as compared with regular insulin.

The more recent preparations with calcium and zinc appear to be more effective than the original protamine insulin. However, further experience will be necessary before their superiority can be expressed statistically.

Summary. From our experience it appears that protamine insulin presents a very definite improvement over regular insulin in the treatment of diabetic patients on a balanced diet. It is possible to reduce both the number of units and the number of injections daily and at the same time to maintain the blood sugar at a more constant level. The feeling of general improvement reported by the patient is gratifying.

Patients who have been controlled with less than 40 units of regular insulin may be satisfactorily transferred to protamine insulin without hospitalization. In this group, rearrangement of the carbohydrate distribution offers definite advantages. Thus, one-fifth of the day's allowance at breakfast and two-fifths at noon and night shifts the metabolic burden so as to coincide with the delayed action of protamine.

In the group of patients on 2 doses of protamine daily, five-sixths of the day's dosage was administered in the morning and one-sixth at night, spacing the doses 12 hours apart.

The influence of protamine insulin on blood sugar is definitely delayed as compared with that of regular insulin.

TABLE 1.—THE EFFECT ON BLOOD SUGAR OF PROTAMINE INSULIN COMPARED WITH THAT OF REGULAR INSULIN.

Number of minutes after insulin injection at which blood sugar decrease was first noted	15	30	45	60	75	90
Number of examinations with regular insulin	7	3	1	2	0	0
Number of examinations with protamine insulin	2	3	4	3	0	1

The incidence of significant decreases in blood sugar at intervals after administration of regular insulin and protamine insulin is shown. Percentage of fall from the fasting value was much greater after the former.

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NUCLEAR SIZES IN GROWTH DISTURBANCES.

WITH SPECIAL REFERENCE TO THE TUMOR CELL NUCLEUS.

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THE sizes of the cells of a given tissue do not vary irregularly, but they depend largely, as has been shown conclusively, upon the laws of growth (Jacobj, 1935). If a cell divides by *mitosis*, there arise two daughter cells, each of which is of the original size of the mother cell. If the daughter cells divide again, there arise four granddaughter cells, each of which is of the original size of the daughter cells. The total volumes of the three generations are therefore in the proportion of 1:2:4 (Fig. 1, I). If a cell grows by *amitosis*, *i. e.*, by nuclear division without cytoplasmic division, the same proportion results. Also in this case there arise daughter cells of double and granddaughter cells of fourfold the size of the mother cells (Fig. 1, II). The same is true also in so-called "*inner division*" (Heidenhain), *i. e.*, in simple enlargement of a cell without nuclear or cytoplasmic division. Also in this event we observe the proportion of 1:2:4 (Fig. 1, III). As all genuine growth is due to mitosis,

amitosis or "inner division," a given tissue only contains cells whose volumes are within a *geometrical line*. Heidenhain (1923), who was the first to derive this law, therefore called it the *law of growth in constant proportions*.

The reason that this law had not been discovered before is undoubtedly due to the fact that only mean figures had been considered. Only when Jacobj (1925) introduced the variation statistical method into cellulometry could this law be verified. Since the findings of Jacobj have been corroborated in many tissues of animals and plants (Clara, 1928-1933; Voss, 1928; G. Hertwig, 1930-1933; Collin and Florentin, 1930, 1931; Monschau, 1930; Lindschau, 1933; Freerksen, 1933; Birkenmaier, 1934, a.o.), it may be assumed that under physiologic conditions the law of Heidenhain is of universal validity.

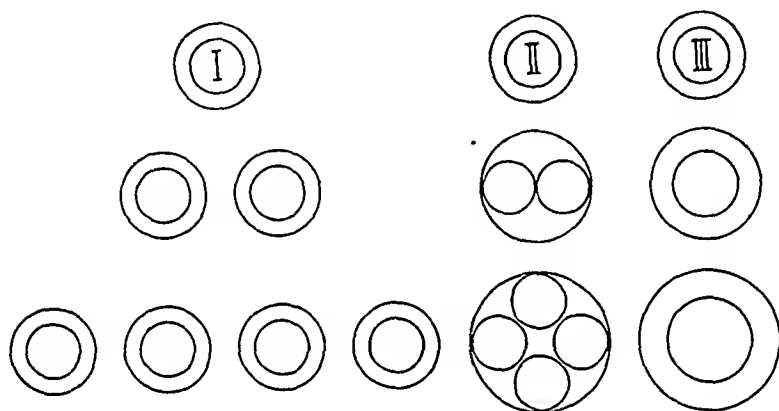


FIG. 1.—Nuclear sizes in mitosis (I), amitosis (II), and so-called "inner division" (III).

On account of the great significance of this discovery, it seemed desirable to extend these investigations to changes which may be included under the term *growth disturbances*, especially as Heiberg since 1907 has frequently stressed the observation that cells of malignant tumors are larger than those of their mother tissues. Measurements were started on normal and cancerous epithelium of tongues, the results of which have been published by my pupil Schmitz (1934). Then Arndt (1935) in our institute reported his findings in regeneration, adenoma and cancer of liver, and Epstein (1935) and Stapel (1935) the results they obtained in measuring cells of salivary glands and their tumors. To this I added data on lymphocytes, lymphoid hyperplasia and lymphosarcoma furnished by my coworkers Repsilber and Vorbeck (1935). Since then further measurements have been carried out by my pupils Carstens, van Hettinga, Kaiser, Kędziorra, Krause, Lohse, Mondry, Neuss, Pentz, Rentzow, Schreiber, Schwermer and Simon, the results of which are the subject of this paper.

Material and Method. The material of our study consists of 230 specimens, half of which were disturbances of growth. Eighty cases were tumors. As the usual methods of fixation and imbedding, especially imbedding in paraffin, lead to shrinkage of the cells up to 30 % and more (Ehrich and Cohn, 1931; G. Hertwig, 1931), only formalin fixed frozen sections (and in a few instances also sections imbedded in gelatine) were used. Jacobj's (1935) statement that it is sufficient to use methods of the same kind to get incontestable comparable data cannot be accepted, for the degree of shrinkage depends not only upon the kind of the fixative and imbedding, but also upon the time of application, the size of the specimens and other factors (Ehrich and Cohn).

For obvious reasons we had to content ourselves with measuring nuclei only. As the nuclear-cytoplasmic ratio of the cells of a given tissue can be regarded as constant, the conclusion may be drawn that the principles drawn from this study can be applied to whole cells too.

To obtain exact measurements, the nuclei, magnified 2500 times, were drawn on paper by means of Edinger's drawing projection apparatus. In every field were drawn all nuclei whose contours stood out clearly. The measurements were carried out by determination of the two largest diameters being perpendicular to each other. After conversion into mikra the volumes were calculated by the simple formula $V = r^3$ (r being $\frac{2d}{4}$), for we were interested in comparable values only.*

In most specimens 1000 nuclei were measured. The total number of nuclei measured amounts to about 220,000.

To find the sizes of the nuclei that are contained in a given tissue it is desirable to enter the values in a table (Table 1) or to plot a curve (Fig. 2). In doing so one obtains one or more peaks that represent the nuclear sizes searched for. As in most tissues two or more sizes are found, the most frequent one is called the *regular class* (Regelklasse, Jacobj). If the study of the regular class conceals other nuclear sizes, as can happen if there are only relatively few large cells in a tissue, one should make special measurements of a selected number of large cells. By this method of Jacobj in most cases the sizes of the larger nuclei can also be brought out.

TABLE 1.—NUCLEAR SIZES OF TONGUE EPITHELIUM. THIS SPECIMEN CONTAINS TWO NUCLEAR CLASSES THE VOLUMES OF WHICH ARE WITHIN A GEOMETRICAL LINE. THE LARGER NUCLEI BEING MORE FREQUENT THAN THE SMALLER ONES REPRESENT THE REGULAR CLASS.

Volumes of nuclei in r^3	22	26	30	34	39	45	51	52	64	71	80	88	97	107
Number of nuclei	40	60	90	70	60	40	70	80	120	100	90	70	60	50

* Only tissues with round nuclei were selected.

The Physiologic Range of the Nuclear Volumes. On reading the papers that have been published on the subject, the impression is gained that it is believed not only that the nuclear sizes of the same organ are constant in different individuals of the same species, but also that those of different organs in the same individual with

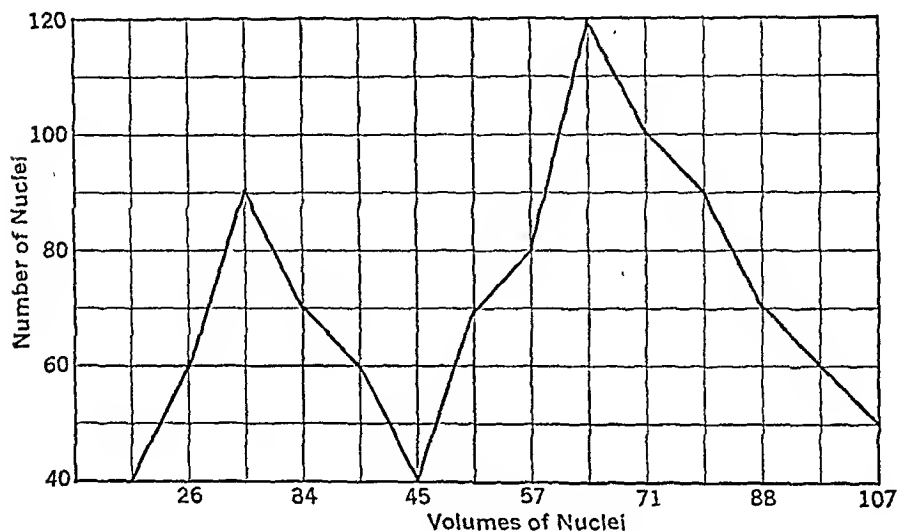


FIG. 2.—The figures shown in Table 1 presented in a curve.

TABLE 2.—VARIATIONS IN NUCLEAR SIZES IN MEN.

Cells.	No. of specimens studied.	Nuclear classes observed (regular class in Italics).	Size of regular class.	
			Radius in μ .	Volume in r^3 .
Epithelium of:				
Tongue	4	N_1 N_2 N_4	4.15-4.4	71.5-85.2
Tonsils	3	N_1 N_2 N_4	3.95	61.6
	9	N_1 N_2 N_4	2.95-3.45	25.7-41.1
Skin	3	N_1 N_2 N_4	2.9-3.5	24.4-42.9
Mucous elements of salivary glands	8	N_1 N_2 N_4	2.9-3.3	24.4-35.9
Serous elements of salivary glands	13	N_1 N_2	2.8-3.1	22.0-29.8
Ducts of mucous glands	11	N_1 N_2 N_4	2.55-3.0	16.6-27.0
Ducts of serous glands	13	N_1 N_2 N_4	2.4-2.9	13.8-24.4
Hypophysis	10	N_1 N_2 N_4	2.5-2.9	15.6-24.4
Prostate	7	N_1 N_2	2.4-2.9	13.8-24.4
Thyroid gland	4	N_1 N_2 N_4	2.45-2.6	14.7-17.6
Resting breast	9	N_1 N_2	2.1-2.8	9.3-22.0
Puerperal breast	4	N_1 N_2	2.5-2.9	15.6-24.4
Lymphocytes	33	N_4 N_2 N_1^*	2.7-1.9	19.7-6.9

* Whereas most cells increase in size during growth, the lymphocytes as other blood cells decrease.

a few exceptions are in the same geometrical line. According to Jacobj (1935) here also exist great, unexpected correlations in that the typical nuclear volumes of different kinds of cells are, as he states, integer multiples of an elementary basal quantum. The reason that the anatomists reached this conclusion is probably because all of them studied only one or a very few organs of the

same kind. If they had studied series of organs, this opinion would not have arisen.

Concerning the first question, namely the *behavior of the nuclear volumes of the same organ in different individuals of the same species*, it can be seen from Table 2 that they are by no means constant. If we disregard the organs of which only 3 to 4 specimens have been measured, and if we disregard the lymphocytes which as we will see behave differently, we find variations of 30 to 80 % (in most cases about 44 to 56 %). The smallest variations were found in the parenchyma of salivary glands, the largest in breasts.

The factors that cause these variations appear to be manifold. A very important factor seems to be the *functional state* of the cells. If we look at the values of *resting breasts* (Table 3) we find that the nuclear volumes increase with increasing age, especially after the menopause, and that after the 65th year of age, which can be regarded as the point when old age begins, they decrease again. As these changes are not in the proportions of the law of growth, which are as has been stated in a geometrical line, *they cannot be an expression of genuine growth, but must be looked upon as changes of simple swelling and shrinkage*. The causes of these changes may be searched for in functional differences or in a changing control of the innersecretory organs. The shrinkage after the 65th year, however, is probably due to *atrophy of old age*.

Concerning the low nuclear sizes of our 21-year-old girl we may have to deal with a starting point of the swelling that increases with age. Whether this is true or not can be disclosed by further studies only.

If we turn now toward our *puerperal breasts* (Table 3), we easily recognize that the nuclei of all cases are much enlarged as compared with the resting breasts of the corresponding ages. As the enlargement amounts from 26 to about 100 %, we may conclude that also here we have not to deal with genuine growth but with simple swelling. The cause of this is certainly of functional or internal secretory character.

That the functional state of the cells is really an important factor in the variations of nuclear sizes is further illustrated by a comparison of the cyclicly functioning breasts with the steadily functioning *prostate*. If we look at Table 4 we find that after puberty the nuclear volumes of the prostate vary very little only. This constancy is in accord with the fact that the prostate is a gland that after puberty works very steadily. Before puberty we find much smaller nuclei. But as the difference amounts to 37 % only, these nuclei cannot belong to a smaller nuclear class. It rather must be suggested that the cells of the prostate during puberty undergo a swelling analogous to the swelling of breast tissue during functionally revolutionary times. This suggestion is in accord with the statement of Stieve, according to which the prostate develops very rapidly during puberty.

TABLE 4.—VARIATIONS IN NUCLEAR SIZES IN NORMAL PROSTATES.
(This table shows the regular class only.)

		Age in years.						
Radius in μ .	Volume in r^3 .	14	17	18	35	49	52	59
Number of nuclei.								
1.6	4.1	12	1	1
1.8	5.8	74	..	1	4	..	2	5
2.0	8.0	170	9	10	23	15	12	24
2.2	10.6	237	51	36	77	34	55	114
2.4	13.8	288	172	126	226	98	108	237
2.6	17.6	243	351	226	324	170	216	312
2.8	22.0	158	314	319	305	216	241	306
3.0	27.0	64	157	220	198	249	216	192
3.2	32.8	21	89	145	105	151	179	64
3.4	39.0	4	28	78	32	101	86	31
3.6	46.7	3	6	26	12	40	48	9
3.8	54.9	1	..	10	4	15	16	2
4.0	64.0	6	1	1	9	..
4.2	74.1	2	..	1
4.4	85.2	4

Whereas in breasts and prostates the factors that cause variations of the nuclear sizes appear to be mainly functional in character, in *salivary glands* other factors also seem to play an important rôle. One of these factors seems to be the *general state of nutrition* or the *kind of death*, for large nuclei were mainly found in large acini and these mainly in well-nourished persons that died suddenly, whereas emaciated persons that died slowly usually showed small acini as well as small nuclei. This finding is in accord with the general opinion that somatic glands are susceptible to atrophy whereas the genetic glands are resistant to a certain degree.

If we turn now to the *lymphocytes* we shall recognize that the much greater variations found in these cells are due to quite different causes. Table 5 shows that in the so-called germinal centers of the lymphatic tissue three nuclear classes occur, the volumes of which measuring $V = 14.4 - 20.4$, $27.7 - 36.8$, and $52.8 - 65.4$ r^3 are in the proportion of 1:2:4. Thus we have to deal with three sizes of lymphocytes that correspond to the small, medium-sized and large lymphocyte of the terminology of my earlier publications (1928, 1931). The regular class was that of the small lymphocytes in all our cases.

If we look now at the solid secondary nodules, pseudo-secondary nodules and lymphoid tissue we find indeed also here in most cases nuclear classes which measuring $V = 25 - 27.6$ and $51.7 - 66.1$ r^3 correspond to the medium-sized and large lymphocytes of the germinal centers. But instead of small lymphocytes with the nuclear sizes of $V = 14.4 - 20.4$ r^3 we find in most cases lymphocytes the nuclear volumes of which show all transitions between $V = 6.6$ r^3 to $V = 12.6$ r^3 . Thus we find sizes that not only are out of the proportions of the other lymphocytes but also show all transitions between the sizes of the small lymphocytes of the germinal centers and the next lower figure of the same geometrical line. If we com-

pare cases of corresponding ages only this fact comes out more distinctly still.

The significance of this finding seems to be clear. If we recall that in germinal centers abundant karyokinetic figures occur whereas in solid secondary nodules, pseudo-secondary nodules and lymphoid tissue these usually are scarce, we may conclude that, in contrast to the large, medium-sized and small lymphocytes of the germinal centers which certainly originate by mitosis, the smaller lymphocytes of the other lymphocellular tissues, that are out of this proportion, are formed by *shrinkage*.

The question why in most cases shrunken small lymphocytes but in some cases those that are not shrunken prevail, will not be discussed here. But it may be stated that the age of the individuals, the periodic occurrence of the lymphopoiesis and the rapidity of formation of lymphocytes probably are factors concerned.

Besides these distinct maxima, there are in a few instances figures that show no maxima at all but wide ridges that reach from the size of the large lymphocytes to that of the medium-sized lymphocytes or from the medium-sized lymphocytes to the small lymphocytes that are not shrunken or from these to the shrunken ones (Table 5). These ridges certainly are an expression of the suddenness by which the transformation of the lymphocyte occurs (Ehrich, 1931). This sudden transformation is a fine example of the rhythmic course of growth phenomena.

If we turn now towards the second question, namely to the *behavior of the nuclear volumes of different organs*, we find (Table 2) that also these show no conformity. If we compare nuclei of the same order we find sizes that show all transitions from $V = 9.3 - 22.0 \text{ r}^3$ to $V = 24.4 - 42.9 \text{ r}^3$. As these sizes differ by more than 100 %, it can be concluded that in different organs nuclei of almost every size can be found.

The causes of this variation are far from being understood. If we recall however that in livers and salivary glands the volumes of the nuclei of the epithelial cells of the ducts and those of the parenchymal nuclei are in the proportion of 1:1.5 (Arndt, Epstein), it may be assumed that *functional differentiation* plays an important rôle.

From all these observations we may conclude that the assumption of the anatomists, according to which the nuclei of a given organ as well as of a given individual are of constant size or integer multiples of an elementary basal quantum, is not correct. In fact, there is an *immense variation not only in the same organ in different individuals of the same species but also in different organs of the same individual*. The factors that cause these variations seem to be manifold. In physiologic variation apparently functional influences play the main rôle.

TABLE 5.—VARIATIONS IN NUCLEAR SIZES OF THE LYMPHOCYTES OF SECONDARY NODULES AND LYMPHOID TISSUE.

(This table shows all maxima observed.)

	Age.	Volume in μ^2 .		
		N ₁ .	N ₂ .	N ₃ .
Flemming's secondary nodules (germinal centers)	8 months	14.8	21.0-57.1
	2 years	14.4	33.6
	4 "	17.2	35.1
	15 "	12.6-36.5	56.0
	16 "	15.2	32.8
	16 "	18.2	33.6
	17 "	16.2	32.0
	19 "	15.6-31.3	52.8
	20 "	16.2	27.7
	24 "	20.2	33.5
	24 "	20.2	36.8
	25 "	10.6-16.6	29.1	56.1
	30 "	10.6-16.6	30.5	56.1
Solid secondary nodules	32 "	19.2	36.8
	38 "	17.2	33.5
	38 "	17.2	62.9
	Newborn	9.6	28.0
	"	10.3	27.7
	"	12.2-16.6	28.0
	"	11.0	28.1
	"	14.3	29.1
	4 days	6.6	56.0
	4 months	7.7	26.4
	9 "	10.3	27.7
	7 years	8.3	26.4
	17 "	12.6	34.4
	19 "	10.7	58.3
	22 "	12.2-15.6	36.8
	78 "	11.4-15.6	31.3	62.8
Pseudo secondary nodules	Newborn	11.0	25.0
	4 days	8.5	25.0
	4 months	11.0	30.5
	7 years	9.5	27.7
	22 "	13.0-15.6	33.5	51.7
Lymphoid tissue	14 months	13.0-15.6	37.6
	8 "	16.2	26.8
	1 year	14.8	32.8
	2 years	12.2	30.6
	16 "	15.7	30.6
	17 "	11.8	32.1
	19 "	15.2	36.8
	22 "	11.8	29.8
	30 "	10.6	29.8
	38 "	14.7
	78 "	12.2-18.6	38.5	66.1

The Nuclear Volumes in Hypertrophy and Atrophy. About the nuclear volumes in hypertrophy and atrophy little is known. Data obtained by the variation statistical method are, as a matter of fact,

available in *hypertrophy of the liver* only. After Clara (1930) had made the observation that in compensatory hypertrophy of the liver, besides the usual nuclei of the sizes N_1 , N_2 and N_4 , the sizes N_8 and N_{16} also occur, Arndt (1935) was able to show that the hypertrophy in liver cirrhosis is also characterized by the fact that the number of the larger nuclei increases at the cost of that of the smaller ones. Whereas in a normal liver he found nuclei of the proportion

$$N_1 = 70\%, N_2 = 19\%, N_4 = 11\%$$

in two cirrhotic livers he found the proportion of about

$$N_1 = 43\%, N_2 = 35\%, N_4 = 13\%, N_8 = 9\%,$$

$$N_1 = 38\%, N_2 = 29\%, N_4 = 27\%, N_8 = 4\%, N_{16} = 2\%$$

If we compare these data with findings we obtained in *hypertrophy of the prostate*, we find very similar relations. Whereas our normal prostates showed nuclei of the mean proportion of about

$$N_1 = 83\%, N_2 = 17\%$$

in our hypertrophic prostate we found the proportion of about

$$N_1 = 30\%, N_2 = 68\%, N_4 = 2\%$$

The only difference in Arndt's and our cases is one of degree. Whereas in his cases the number of the larger nuclei ($N_2 - N_{16}$) increased about 27 to 32%, in our cases the increase amounted to 53%. The cause of this difference becomes clear, if we consider that an excessive hypertrophy of the prostate, as in our case, represents a much higher degree of hypertrophy than the hypertrophy of the liver in liver cirrhosis.

Thus it can be stated that in hypertrophy of certain organs cells occur, the nuclear sizes of which are integer multiples of the normal sizes, and the frequency of which is shifted from the smaller to the larger ones. As all sizes found were within the proportions of Heidenhain's law of growth, we may conclude that here we have to deal with a true disturbance of growth.

That similar changes occur also in atrophy can be seen from a case of atrophy of the thyroid gland. Whereas four apparently normal glands showed nuclei of the mean proportion of about

$$N_1 = 92\%, N_2 = 7\%, N_4 = 1\%$$

a very atrophic gland showed that of about

$$N_1 = 99\%, N_2 = 1\%^1$$

These figures show clearly that in atrophy of certain organs the reverse occurs of what we just have seen in hypertrophy.

In other cases of hypertrophy and atrophy, however, the outstanding features are changes that are of a quite different nature. If we regard the enlargement of the breasts during pregnancy described in the foregoing chapter as a functional hypertrophy and its diminution in old age as a senile atrophy, we can conclude that in certain organs hypertrophy and atrophy is due at least in part to simple swelling and shrinkage of the cells. This change, however, cannot be looked upon, as has been pointed out already (pp. 775-779),

¹ In this case also a shrinkage of the nuclei could be noted.

as a true growth disturbance, but rather should be called a functional or nutritional variation.

If we turn to the types of hypertrophy and atrophy that usually are called *hyperplasia* (numerical hypertrophy) and *numerical atrophy*, we again find different changes. The outstanding feature in these cases is an increase and decrease of the number of the cells, whereas a change of the size plays a minor rôle. If we compare the nuclear sizes we obtained in 3 cases of *lymphatic hyperplasia* (hyperplasia with the formation of so-called germinal centers) and in 6 cases of *lymphoid hyperplasia* (diffuse hyperplasia without secondary nodules) with those of normal germinal centers and lymphoid tissues (Table 6), we find a close concordance. Concerning the frequency of the three nuclear classes a shift from the small lymphocytes to the larger ones could not be detected in lymphoid hyperplasia. In lymphatic hyperplasia, however, we observed a definite increase of the number of the medium-sized lymphocytes at the cost of the small ones, which in one case even led to a prevalence of the medium-sized lymphocytes. From these findings the conclusions may be drawn, *that in hyperplasia we have to deal with an increase in the number of cells mainly, but that in certain cases there occurs also a shift from the smaller to the larger cells, similar to the shift that has been observed in hypertrophy of the liver and prostate.*

TABLE 6.—THE NUCLEAR SIZES OF LYMPHOCYTES IN LYMPHATIC AND LYMPHOID HYPERPLASIA.

	No. of specimens.	Volumes of nuclear classes.		
		N ₁ .	N ₂ .	N ₃ .
Flemming's secondary nodules:				
Normal	15	14.4-20.2	27.7-30.8	52.8-65.4
Lymphatic hyperplasia . . .	3	14.7-16.6	27.7-31.3	57.1
Lymphoid tissue:				
Normal	11	10.6-12.2		
		14.7-16.2	29.8-38.5	57.1-66.1
Lymphoid hyperplasia . . .	7	9.3-12.2		
		14.7-16.2	27.0-31.3	

Specimens of *numerical atrophy* have so far not been studied. But there can be no doubt that it is characterized by a decrease in the number of cells.

From all these observations it can be seen that there are several avenues by which hypertrophy and atrophy can arise. In some cases we have to deal with true growth disturbances (increase or decrease in size or number of cells in the proportion of Heidenhain's law of growth) and in others with changes that should be headed by the term of functional or nutritional variations (simple swelling or shrinkage of cells outside of these proportions). In many cases two of these three avenues are chosen, one overlapping the other.

The question why in some cases the one and in others another avenue is chosen, can be answered in part at least. As hyperplasia

and numerical atrophy are found in tissues only that show a great regenerative ability (tissues with unstable elements (Levi)), whereas the others are observed in tissues with little or no regenerative ability (tissues with stable or imperishable elements (Levi)), there can be no doubt that regenerative ability or its cause is one of the factors concerned. The question however as to why the increase and decrease of the size of the cells in some cases is due to true changes of growth and in others to simple swelling and shrinkage, cannot be answered with certainty. But as the former has been observed only in tissues, the nuclear sizes of which as well as their function appear to be very steady, whereas the latter was found in glands the nuclear sizes of which as well as their function show great periodical changes, it suggests itself that it is the steadiness, or the functional variability which plays the deciding rôle. Whereas organs which react even normally with swelling and shrinkage of their cells will do so also in pathologic conditions; organs which have no such abilities can react only with a new growth within the proportion of Heidenhain's law of growth.

In summary we may conclude therefore that *hypertrophy and atrophy can be due to a change in size or number of the cells in the proportions of Heidenhain's law of growth (true growth disturbances) or to a simple swelling or shrinkage (functional or nutritional variations). Which of the avenues is chosen, depends largely upon the regenerative ability of the tissues and probably upon the varying ability of functional swelling or shrinkage of their cells.*

The Nuclear Volumes in Benign Tumors. In many papers it has been stated that the nuclei of benign tumors are larger than those of their mother tissues. Reliable data however are scarce. Also, as Arndt (1935) has pointed out, the figures given by Heiberg do not stand adverse criticism.

The first to study the nuclei of benign tumors by means of Jacoby's method was Arndt (1935) in our institute. He found that the single nuclear classes of liver adenomas were to be sure in the proportion of Heidenhain's law of growth, but that they were distinctly larger—the enlargement amounting to about 25 %. Then my pupil Stapel (1935), who measured several tumors of salivary glands, reported that the nuclei of the so-called mixed tumors, which, according to our view, must be looked upon as adenomas of the serous elements of the salivary glands were about 20 to 25 % larger than those of their mother cells.

In the meantime we have studied some more benign tumors (see Table 7). From this table it can be seen that papillomas of the skin as well as cystic tumors and fibroadenomas of the breast consist of cells, the nuclei of which are bigger than those of their mother cells. As the latter vary a great deal, exact figures for the increase cannot be given. But it is beyond doubt that in these tumors also the increase does not exceed 50 %. As these figures do not reach

the proportions of Heidenhain's law of growth (figures of a geometrical line), we can conclude that the enlargement of the nuclei of benign tumors is not due to true growth but rather to a simple swelling, analogous to the simple swelling observed in hypertrophy. This conclusion is not contradictory to the fact that benign tumors as a whole are growth disturbances, for their outstanding feature certainly is an increase in the number of their cells.

TABLE 7.—NUCLEAR SIZES IN BENIGN TUMORS.

	Measurements made by:	No. of specimens studied.	Nuclear class observed (regular class in <i>italics</i>).	Size of regular class, volume in r^3 .
Epithelia of skin	Kaiser	3	N_1 N_2 N_4	24.4–42.9
Papilloma of skin	Kaiser	1	N_1 N_2 N_4	51.7
Serous epithelia of salivary glands .	Epstein	13	N_1 N_2 (?)	22.0–29.8
So-called "mixed tumor" of parotid	Stapel	4	N_1 N_2 N_4	29.8–32.8
Epithelia of liver parenchyma . .	Arndt	4	N_1 N_2 N_4	28.4–37.6
Liver cell adenoma	Arndt	4	N_1 N_2 N_4	34.3–46.7
Epithelia of resting breast . . .	van Hettinga	9	N_1 N_2	9.3–22.0
Epithelia of puerperal breast . .	van Hettinga	4	N_1 N_2	15.6–24.4
Cystic breast	Pentz	4	N_1 N_2	20.3–30.6
Fibroadenoma of breast	Pentz	4	N_1 N_2	20.3–27.9

The cause of the swelling of the nuclei in benign tumors cannot as yet be detected. That we have not to deal with functional factors, as in hypertrophy, seems to be clear. If the assumption of Wermel and his associates (1932–1934) is correct, *i. e.*, that the swelling of nuclei in tissue cultures is due to the loss of control by the whole organism, then the idea is suggested that in benign tumors we might have to deal with cells that are excluded from this control. But whether this is true or not must be left to further studies.

The Nuclear Volumes in Malignant Tumors. It has been stated frequently that the cells of malignant tumors are larger than those of their mother tissues. Especially Heiberg has stressed this point again and again (1907–1935). Whereas in earlier communications he merely stated this finding, in later publications he attached a profound significance to it, namely, that this was due to tetraploidy, *i. e.*, doubling the number of chromosomes, and that this tetraploidy was the cause of the greater energy of growth of malignant tumors. If these papers have not found the echo they deserved, this was certainly due to the rather unreliable method Heiberg used. Had he used the variation statistical method, cancer research perhaps would have taken quite another course in the last 20 years.

The first who used the variation statistical method in measuring the nuclei of malignant tumors was my pupil Schmitz (1930). He found that in carcinoma of the tongue *all* nuclei were *doubled* or

quadrupled in size, so that we felt we were entitled to speak of a change to another level of size not merely of cells but of the *whole epithelial tissue*. Then Arndt (1935) in our institute reported the same findings in carcinomas of the liver, whereas my pupil Stapel (1935), who measured tumors of the parotid gland, was even able to show that by this method a differential diagnosis between carcinomas of the acinar cells and of the ducts could be made. Finally I (1935) reported that measurements of lymphosarcomas gave results in full accord with those of carcinomas.

Schairer (1935), the only author who has since taken up these investigations, using the variation statistical method, was not successful because he used material differently fixed and imbedded, and because he overlooked the physiologic range of normal nuclear sizes. Therefore his statements need not be discussed here.

Since our preliminary reports we have measured many more malignant tumors. In the case of the sarcomas—with the exception of our lymphosarcomas, which I have discussed already (1935)—the mother cells could not be made out; therefore only our carcinomas will be considered here (see Table 8). It may be emphasized that these data are not selected but comprise *all* carcinomas measured by us.

TABLE 8.—NUCLEAR SIZES IN MALIGNANT TUMORS.

	Measurements made by:	No. of specimens studied.	Nuclear classes observed (regular class in Italics).	Size of regular class volume in r^3 .
Epithelium of skin	Kaiser	3	N_1 N_2 N_4	24.4–42.9
Cancer of skin	Kaiser	4	N_1 N_2 N_4 N_8	64.7–95.8
Basalioma of skin	Kaiser	2	N_2 N_4 N_8	40.2–42.0
Cancer of lip	Lohse	1	N_2 N_4 N_8	83.7
Malignant papilloma of anal region	Lohse	1	N_2 N_4 N_8	95.8
Epithelium of tongue	Schmitz	4	N_1 N_2 N_4	71.5–85.2
Cancer of tongue	Schmitz	4	N_2 N_4 N_8	140.2–192.2
Cancer of tongue	Schmitz	1	(?) N_8 N_{16}	344.3
Epithelium of tonsils	Schreiber	9	N_1 N_2 N_4	25.7–41.1
Epithelium of tonsils	Schreiber	3	N_1 N_2 N_4	61.6
Cancer of tonsils	Kendziorra	2	N_2 N_4 N_8 N_{16}	59.3–66.4
Serous epithelium of salivary glands	Epstein	13	N_1 N_2 (?) N_8	22.0–29.8
Papillary cancer of salivary glands	Stapel	1	N_2 N_4 N_8	53.8
Epithelium of salivary gland duct	Epstein	13	N_1 N_2 N_4	13.8–24.4
Adenocarcinoma of gland duct .	Stapel	4	N_2 N_4 N_8	35.9–42.0
Epithelium of liver parenchyma .	Arndt	4	N_1 N_2 N_4 N_8	28.4–37.6
Cancer of liver parenchyma . .	Arndt	3	N_2 N_4 N_8	61.6–71.5
Epithelium of prostate*	Deysing	6	N_1 N_2 N_4	17.6–24.4
Cancer of prostate	Deysing	1	N_2 N_4 N_8	40.2
Cancer of prostate	Deysing	1	N_2 N_4 N_8	116.1
Epithelium of resting breast . .	van Hettinga	9	N_1 N_2	9.3–22.0
Epithelium of puerperal breast .	van Hettinga	4	N_1 N_2	15.6–24.4
Solid carcinoma of breast . . .	Drücke	2	N_2 N_4 N_8	36.8–43.9
Solid carcinoma of breast . . .	Drücke	1	N_2 N_4 N_8	70.3
Adenocarcinoma of breast . . .	Drücke	1	N_2 N_4 N_8	40.4
Scirrhus carcinoma of breast . .	Drücke	2	N_2 N_4 N_8	40.4–47.8
Scirrhus carcinoma of breast . .	Drücke	1	N_2 N_4 N_8	92.7
Scirrhus carcinoma of breast . .	Drücke	2	N_2 N_4 N_8	27.9

* One case before puberty left out (see Table 4.)

Looking over Table 8 we easily discern that, with the exception of our basal-cell carcinomas of the skin and of 2 of our cases of scirrhus of the breast, all our carcinomas show nuclear sizes that differ from those of their mother cells by the fact that they are doubled (in 30 cases) or quadrupled (in 4 cases). This comes out particularly well if we compare the sizes of the regular classes. As in no tumor nuclei were found the sizes of which corresponded to those of the lowest nuclear class of the other tissues, we can state that we are not entitled to speak of a simple shifting as observed in hypertrophy, but that we must speak of a *fundamental change to another level of size*—the levels being figures of a geometrical line.

Concerning our exceptions, it can be easily seen that the nuclei of our basal-cell carcinomas are also of double size, if we compare them not with the regular class of the skin epithelium but with the basal cells from which these tumors are derived. In our 2 exceptional cases of scirrhus of the breast, however, the nuclei are actually only 50 % larger than those of their mother cells. But if we consider that in a scirrhus we have to deal with a tumor that is composed to a large extent of a very dense and firm connective tissue, which physically counteracts the expansion of the single tumor cells, then we safely can conclude that also these cases are no true exceptions, but variations due to the particular properties of scirrhus.

We can state therefore that malignant tumors are characterized by doubling or quadrupling of the sizes of their nuclei. A greater variability in the sizes of the individual cells certainly plays an important rôle too, the essential difference however is the turn into a higher level of size—a doubling or quadrupling.

The question whether the reverse is also true, namely, that doubling or quadrupling is characteristic of malignant growth, must be answered in the negative, however, since in a case of puerperal breast and benign goiter we found a similar change. But whereas in hypertrophy we had to deal with a *gradual* swelling or shifting of the cells, in cancer we have a *sudden turn, a jump into a higher level with no transitions whatever*.

Concerning the *pathogenesis* of the malignant cells no satisfactory explanation can be given yet. But since it is well known that the size of the nuclei with the exception of the functional or nutritional variations largely depends upon the quantity of chromosomes (Boveri, 1914; Jacoby, 1926; G. Hertwig, 1930-1932), it seems to be certain that this question and with that the question of carcinoma is a chromosomal one.

If we have two cells the one of which is double the size of the other, this doubling can be due to a double number or to a double size of the chromosomes. In the first case we speak of polyploidy, in the latter of polymery.

Whereas in normal germ cells polyploidy as well as polymery are said to occur (G. Hertwig), in normal somatic cells polyploidy has

not been demonstrated yet. Therefore the larger cells of the geometrical lines, which arise by "inner division," are supposed to be polymer in character (Jacobj).

The question whether polymer cells under normal conditions can divide again by mitosis, cannot be answered yet with certainty. In careful studies of regeneration of the liver Clara (1931) found mitoses almost exclusively in the smallest cells of the periphery of the lobules, which probably are monomer in character; in the very few larger cells that showed mitoses he found approximately the double number of chromosomes; but as his animals were poisoned by phosphorus, the possibility cannot be excluded that these cells had arisen by fusion, instead of by inner division, especially since he found other abnormalities of mitoses (see Politzer, 1934).

Also the occurrence of the so-called multiple succedan divisions, which lead to a reduction in size and which are best observed in germ and blood cells, does not help to solve this question; for in the case of germ cells we have to deal with heterotypic mitoses, whereas in blood cells satisfactory chromosome studies are not available. It may be mentioned in this connection that in leukemia haploid mitoses have been observed (Isaacs, 1930; Groat, 1933).

Concerning the chromosomes in malignant tumors many data are available. The principle findings, that have been confirmed again and again are diploid, tetraploid, octoploid, and even higher polyploid mitoses often in one tumor (Winge, 1927, 1930); Heiberg and Kemp, 1929; Lewis and Lockwood, 1929; Levine, 1929, 1931; Goldschmidt and Fischer, 1930; Hirschfeld and Klee-Rawidowicz, 1930; Andres, 1932; Alexenko and Natansohn, 1933). But as no data have been accumulated correlating the number of chromosomes to the size of the nuclei, and as no chromosomal measurements have been published, so that we do not know whether the chromosomes were monomer or polymer in character, no conclusions as to the significance of these findings can be drawn. It might be that Winge (1927) and Jacobj (1929) are correct when they assume that it is a heterotypic mitosis that starts malignant growth. Or it might be that Arndt (1935) is correct, who believes that polymer cells normally do not divide by mitosis, but that if they do, then cancerous cells develop. Especially the latter theory is very tempting, of course, but it cannot be excluded yet that a polymer cell cannot normally divide by mitosis. According to our present knowledge, therefore, we only can state that it seems to be established that the pathogenesis of the malignant cells is a chromosomal question, and that probably we have to deal with a derailing from the normal track of growth during mitosis or inner division.

Concerning the *etiology* of malignant tumors no new information can be expected by these studies. But attention may be paid to the fact that almost all agents that produce cancer are known also to produce chromosomal disturbances and *vice versa*.

In conclusion, therefore, we can say that *malignant growth is characterized by cells that are double or fourfold the size of their mother cells, and that this doubling or quadrupling probably is due to a derailing from the normal track of growth probably during cell division. The malignant cell, therefore, is a special cell and not an embryologic cell, for these belong to the smallest cells observed. But if the malignant cell is a special cell and if its specialty is its double or fourfold size, then we safely can conclude that the double or quadruple size of the malignant tumor cells is an anatomical expression of the anaplasia or kataplasia of malignant tumors so long searched for.*

Summary. The present report is based upon the measures of 220,000 nuclei of 230 specimens, half of which were growth disturbances.

In all tissues studied, normal as well as pathologic, several nuclear classes were found the sizes of which were in the proportions of Heidenhain's law of growth.

The nuclear sizes of *normal tissues* are by no means constant; they vary not only in the same organ in different individuals, but also in different organs of the same individual. In physiologic variations apparently functional influences play the main rôle.

In *hypertrophy* and *atrophy* several mechanisms are involved. In certain organs we find an increase or decrease in the size of the nuclei in the proportions of Heidenhain's law with a shift from the number of the smaller to the larger cells or *vice versa* (liver, prostate). In other organs we merely observe an increase or decrease in the number of cells with or without change of their size (lymphatic and lymphoid tissue). In still others we mainly find a simple swelling or shrinkage outside of the proportions of Heidenhain's law (breast, thyroid). Which of these avenues is chosen depends largely upon the regenerative ability of the tissues and probably upon the ability of functional swelling or shrinkage of their cells.

Benign tumors are characterized by cells larger than their mother cells. The enlargement is due to simple swelling and not to true growth.

Malignant tumors are characterized by cells which are double or fourfold the size of their mother cells, and which probably arise by derailing from the normal track of growth during cell division. The malignant tumor cell is not an embryologic cell, but a special cell that occurs in malignant tumors only. The double or quadruple size of these cells is an anatomical expression of the anaplasia or kataplasia of malignant tumors so long searched for.

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THE MECHANISM OF INACTIVATION OF MERCURIAL ANTISEPTICS BY SERUM, AND ITS IMPLICATIONS REGARDING THE POSSIBILITY OF INTRAVENOUS ANTISEPSIS.

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THE hope of achieving direct chemical destruction of bacteria within the humors of their hosts has fascinated bacteriologists since the beginning of the science. So compelling indeed has this hope been that its realization has been sought at times immediately and empirically with too little consideration of the determining conditions involved. That the result has been disappointing should not occasion surprise.

The present investigation began with the attempt to prepare a serum-mercurial compound suitable for intravenous antiseptics. The failure of our therapeutic experiments, like those of Birkhaug and others,¹ compelled analysis of the chemical system comprising germicide, bacteria and serum.

A method has been developed for quantitative comparison of the bactericidal action of antiseptics, under various conditions.

This has permitted determination of the relative velocities of reaction between bacteria and mercurial and between serum and mercurial, the magnitude of the effect of serum on bactericidal action, and the type of reaction between mercurials and serum.

Comparison of the equivalent bactericidal action of various mercurials on bacteria suspended in 80% serum and in saline solutions has shown that from 300 to 1400 times the concentration of mercurial is required to exert equivalent bactericidal action in the presence of serum. Combination between serum and antiseptic has usually been assumed to occur, but had never been rigorously investigated. When a method of purifying such compounds was devised, they were found to be non-ionic and devoid of bactericidal action.

Methods and Materials. *Quantitative Method for Comparing the Bactericidal Power of Disinfectants.* The usual modifications of the Rideal-Walker method were unsatisfactory for our purpose as they depend on determining a point in concentration and time when no organisms survive. For the sake of comparison it was necessary to know the percentage surviving at any time. Plating experiments were essential for this purpose. For this reason a more accurate method of plating the organisms used was necessary. This allowed a closer mathematical approximation of the effect of serum on the antiseptic used.

The culture used was a smooth, non-motile, laboratory strain of *Eberthella typhosa* (0 901)² grown for 18 hours in extract broth at an initial pH of 7.0. It was centrifuged and resuspended in normal saline at a pH which was carefully adjusted to the first visible change of phenol red (pH 6.8). A slight deviation in the degree of acidity will kill many organisms in the time required to complete the experiment. Dilutions of the disinfectants were made with volumetric flasks and pipettes which had been carefully calibrated. The culture was successively diluted so that control plates showed about 500 colonies. This was a dilution of about 1:10,000 of the original culture. This number of colonies approximated a true statistical picture and was not too large to make counting of the total number of colonies on the plate tedious. That the number of organisms in the suspension on which the antiseptic is allowed to act is of importance can be seen in Fig. 1. Where the number of organisms is increased from 150 to 680, there is an increase in the killing time. Therefore, when comparing the activity of any antiseptics, the number of organisms in the suspension must be rigidly controlled.

Normal horse serum of the same lot was used throughout all the experiments. This is essential as it has been found that the effect of normal rabbit serum and of immune horse serum on bactericidal action of an antiseptic is appreciably different from that of normal horse serum. Meat-extract agar at a pH of 7.0 was used in doing all of the plating. Equal volumes of the suspension of the organisms in saline and the solution of the antiseptic being investigated were allowed to stand at room temperature. The solution of the antiseptic was twice the concentration being investigated to allow for the dilution with the suspension of bacteria. At predetermined intervals 0.2 cc. of the mixture was introduced into 10 cc. of broth, thoroughly mixed by shaking, and then 0.5 cc. of the broth dilution was placed in a Petri dish. After 10 cc. of agar was added, the plate was carefully rotated to insure thorough mixing.

When the effect of serum on antiseptic action was being investigated, 0.2 cc. of the suspension of the organisms was mixed with 1.6 cc. of serum

and 0.2 cc. of a solution of the antiseptic added. The antiseptic was ten times the concentration being investigated in order to allow for the dilution. This gave a concentration of 80% serum. Samples (0.2 cc.) were withdrawn at predetermined intervals, diluted in broth, and plated in the usual manner. This method of plating diluted any excess antiseptic a thousandfold, which is far beyond the killing range of the concentration of the antiseptics studied. All plates were counted after an interval of 4 days in the incubator at 37° C.

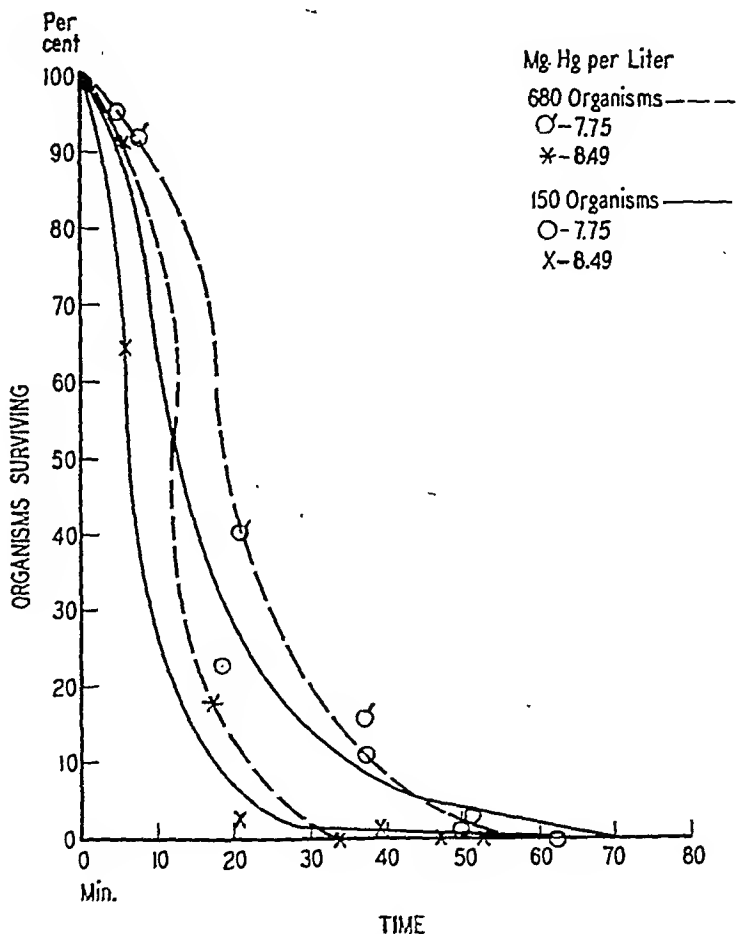


FIG. 1.—Effect of number of organisms on bactericidal action of bichlorid of mercury in serum.

Curves are then made in which the number of surviving colonies are expressed as percentage of the controls for various concentrations of the antiseptic. These percentages are plotted against time (Figs. 2 to 9 incl.). From points on these survival curves graphs are made representing the time and concentration at which various percentages of the organisms survive in different dilutions of the antiseptic, each line representing the same percentage of survivors (Figs. 10 and 11). They show the effect of the concentration on the killing power of the antiseptics studied. As any of

the curves representing per cent survival of the organisms at various times and concentrations form a straight line, a comparison of the antiseptics can be made, using any point on these curves. The 50% survival curve appears to give the best basis for comparison from the standpoint of statistical accuracy. A comparison of the 50% survival concentration at any desired time can be read from the curve. The selection of such a specific time will depend on the rate of activity of the class of antiseptics studied. This type of comparison is much more satisfactory than a mere inspection

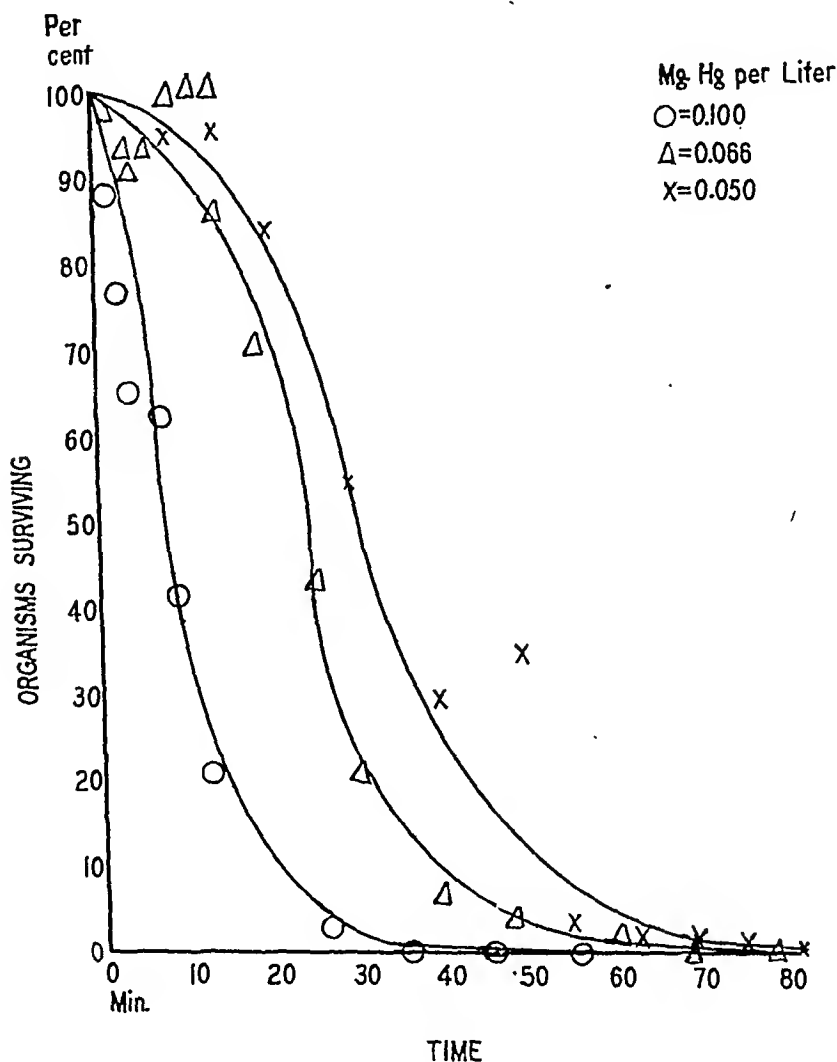


FIG. 2.—Bactericidal action of mercurial M in saline.

of time-survivorship curves of any antiseptics, as the latter are not usually superposable.

The accuracy of the above method as determined by the colony counts of plates made under identical conditions is approximately 10%. By this method it had been possible to construct and compare curves with sufficient accuracy to study: 1, the effect of the number of organisms on the position of the time concentration curves; 2, the relative speeds of reaction between bacteria and various mercurials; 3, the magnitude of the effect of serum on bactericidal action; 4, the type of reaction between mercurials and serum.

(Evidence has been obtained showing this to be an addition reaction, and not an adsorption reaction.)

Mercurials. Metaphen, Mercurial M, Merthiolate and Mercurochrome were not known to be chemical entities, so they were analyzed for mercury, and all figures are based on their mercury content. Mercuric chlorid (Merck reagent) was used, for comparison, since the chlorid ion is known to be non-toxic. Mercurochrome was obtained from Hynson, Westcott

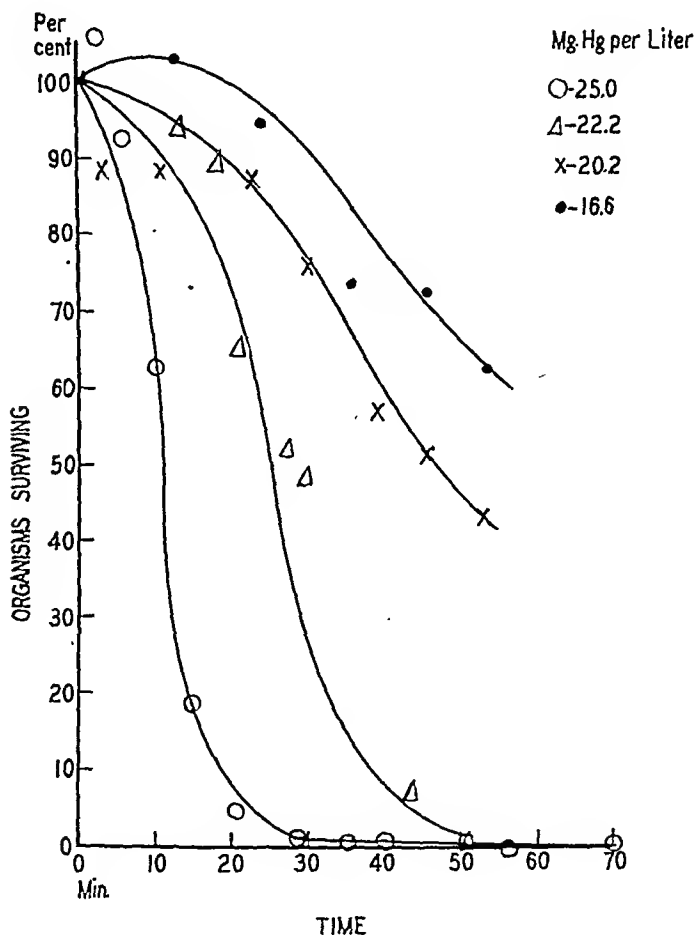


FIG. 3.—Bactericidal action of mercurial M in serum.

and Dunning. Merthiolate came from Eli Lilly and Company, and was marked "Released for use as a biological preservative." In some of the experiments a solution of Metaphen, 1:500, from the Dermatological Research Laboratories was used. Since we were unable to obtain any Metaphen powder from them when we began this investigation, Dr. A. Proskouriakoff* very kindly synthesized for us a mercurated nitro-ortho-

* We wish to thank Dr. Proskouriakoff not only for the compound but for giving us the benefit of his long experience with the chemistry of mercurials on the occasions when we asked his advice.

cresol in the laboratory at Jefferson Hospital. This will be designated Mercurial M for convenience. In our hands this behaved like Metaphen both in respect to chemical reactions and bactericidal activity, within the limits of experimental error. As experiments with Mercurial M and Metaphen are very similar, only Mercurial M will be reported.

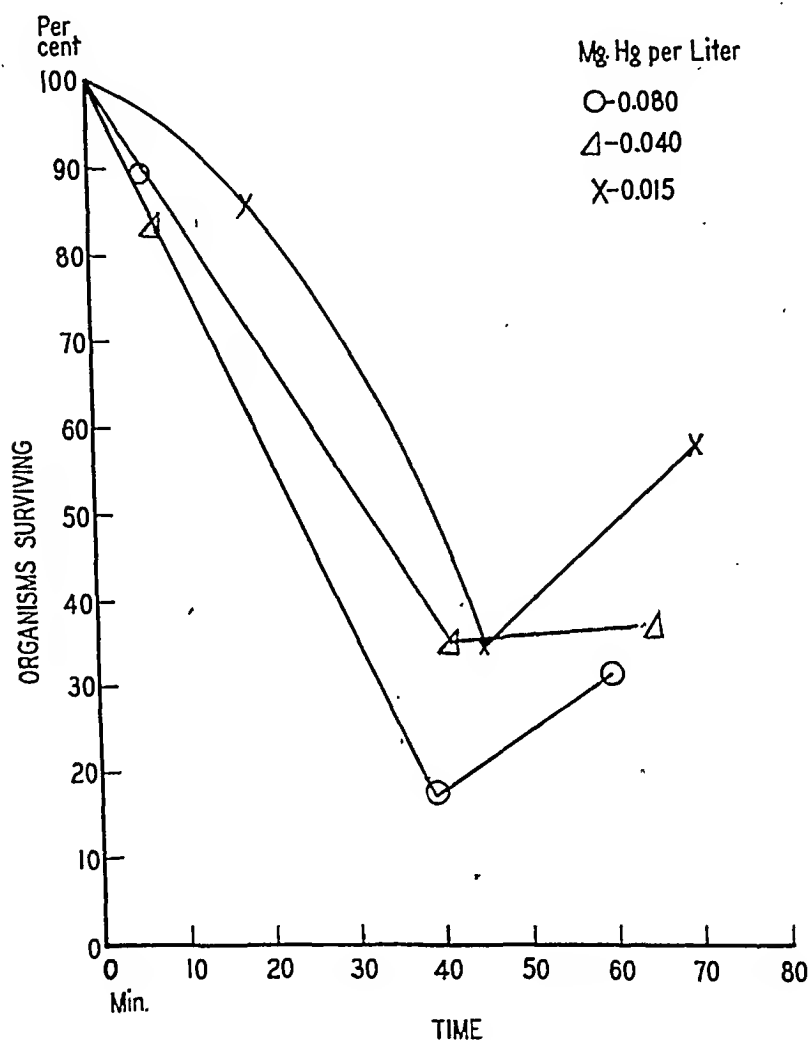


FIG. 4.—Bactericidal action of merthiolate in saline.

Serum. One lot of pooled normal horse serum obtained from Sharp & Dohme, at Glenolden, was used throughout the experiments. Due to the necessity of water as a solvent of the mercurials, only a concentration of 80% serum could be used in the plating experiments.

Temperature. All of the reactions were allowed to take place at laboratory temperature. The slight fluctuations in temperature were not of sufficient importance to be taken into account.

Results. 1. *Relation Between Antiseptic Action and Time and Concentration.* In Figures 2 to 9 we have plotted curves showing the effect of time and concentration on the bactericidal action of 4 of the mercurials studied, in saline and in serum. The concen-

tration has been plotted in milligrams of mercury per liter. Concentrations necessary to kill 50% of the organisms in 30 minutes can be compared to show the relative value of the antiseptics. Figure 2 shows that there is a rapid falling off in the efficacy of Mercurial M with a decrease in concentration, but even so, 50% of the organisms are killed in a dilution of 1 in 6,000,000 in 30 minutes.*

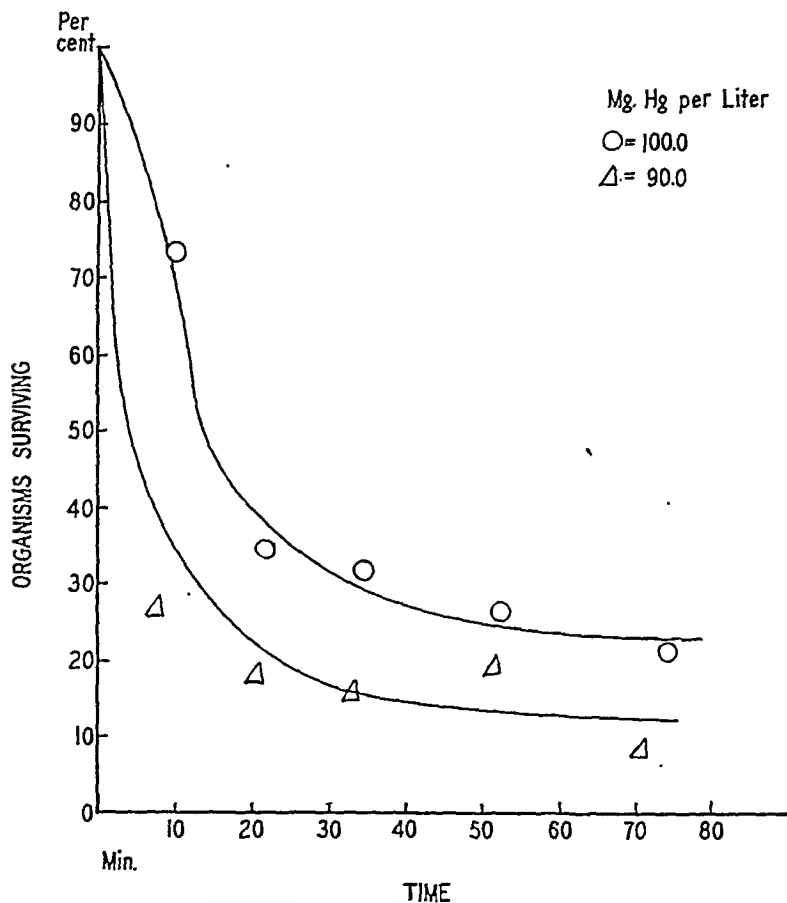


FIG. 5.—Bactericidal action of merthiolate in serum.

To produce this same effect in the same time in serum (Fig. 3), a concentration of 1 in 17,000 is required. This is a difference in concentration of approximately 340 times. A comparison of the time and concentration at which any certain per cent of organisms survive can readily be made by an inspection of survival curves derived from time-concentration curves (Figs. 2 to 9). Such survival levels for Mercurial M in saline and in serum are shown in

* A similar curve is obtained for Metaphen.

Figures 10 and 11. The 50% survival level curve is derived by plotting points representing the time at which 50% of the organisms survive for each concentration used, the slope of the line being determined by the time required for each concentration of the antiseptic to exert its effect. The other survival levels are determined in the same manner. With the aid of these curves, the time and concentration at which any per cent of the control organisms survive can be observed.

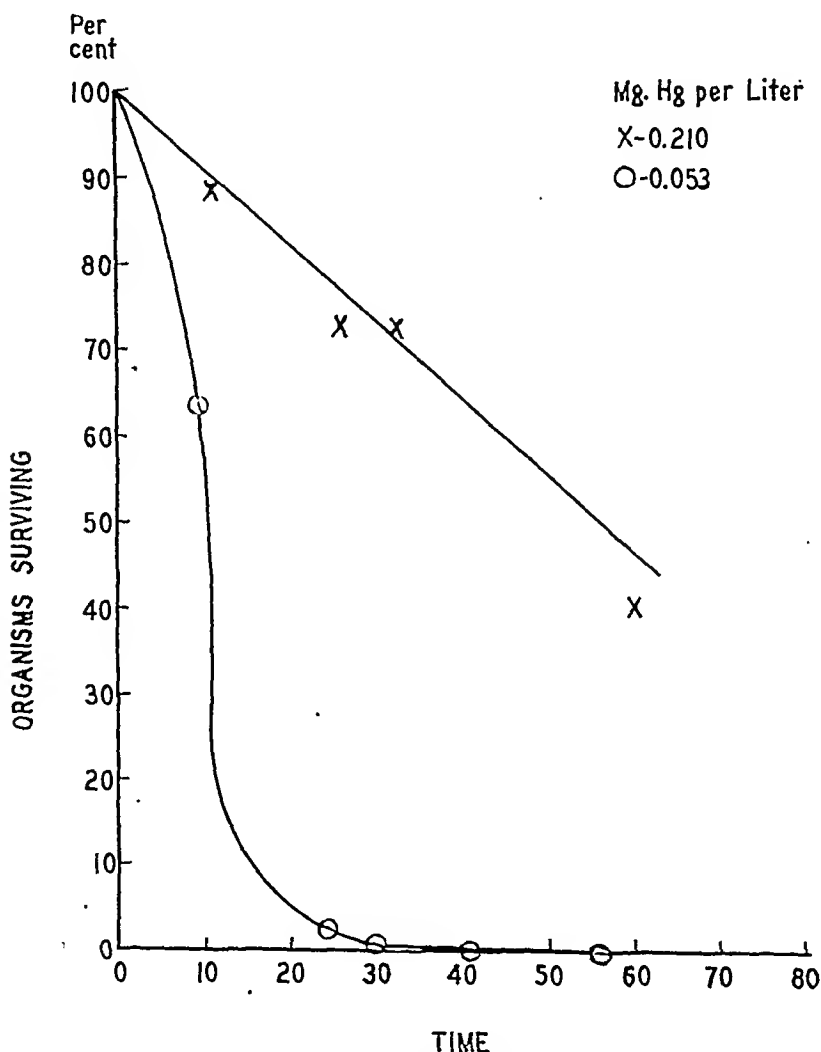


FIG. 6.—Bactericidal action of mercuriochrome in saline.

Points on each survival level represent the same degree of reaction between a mercurial and bacteria, or between a mercurial and bacteria plus serum, for different times and concentrations. Curves drawn through such points represent the relationship between time and concentration for the same degree of reaction. As these survival levels form straight lines, the time of reaction is inversely

proportional to the concentration for any survival level, and therefore these reactions are addition reactions of the first order, and not adsorption reactions. In the latter case the lines would tend to be curved, and would represent reactions of a zero order. As it has been shown that the reactions between a mercurial and bacteria and between a mercurial and bacteria plus serum are strictly chemical addition reactions, the data concerning such reactions can

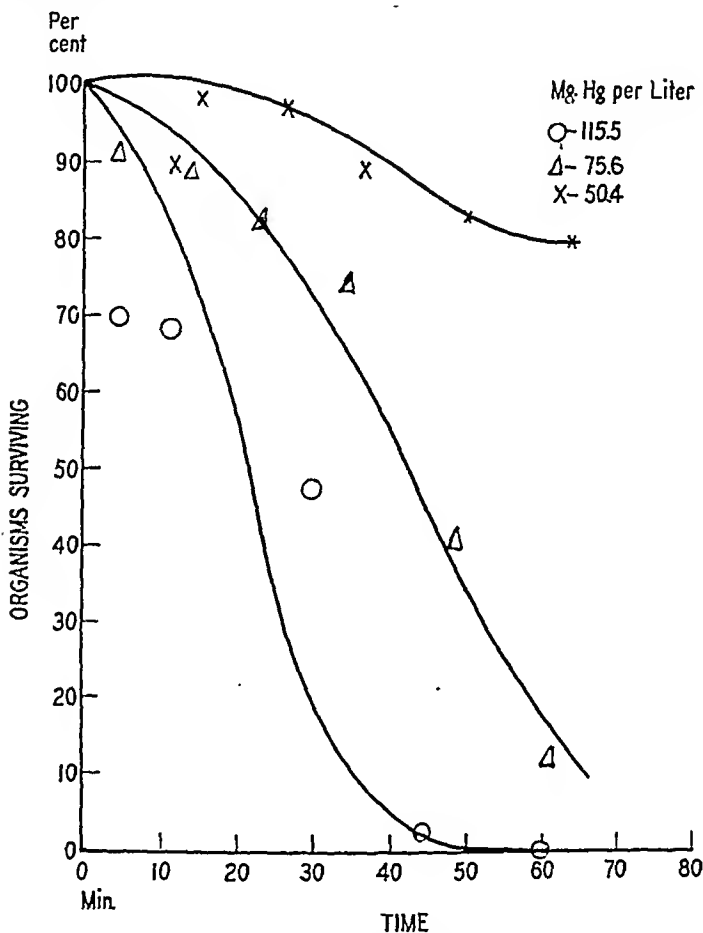


FIG. 7.—Bactericidal action of mercurochrome in serum.

be treated as such, and analyzed from a mathematical viewpoint. Thus survival levels can be considered as vectors of a degree of reaction. The different survival level curves for the reactions of bacteria with Mercurial M in saline are almost parallel, indicating the same relationship as to time and concentration for each survival level. When the time-concentration relationship is the same for each degree of reaction only one reaction is taking place, as no two reactions take place at exactly the same rate.

The survival levels showing the reactions of Mercurial M with bacteria in serum (Fig. 11) are not parallel, indicating two different reactions of different rates, which are going on simultaneously. As the additional component of this system is serum, the second reaction going on is between the mercurial and serum. From Figures 10 and 11 it can be seen that much more of the mercurial as mercury

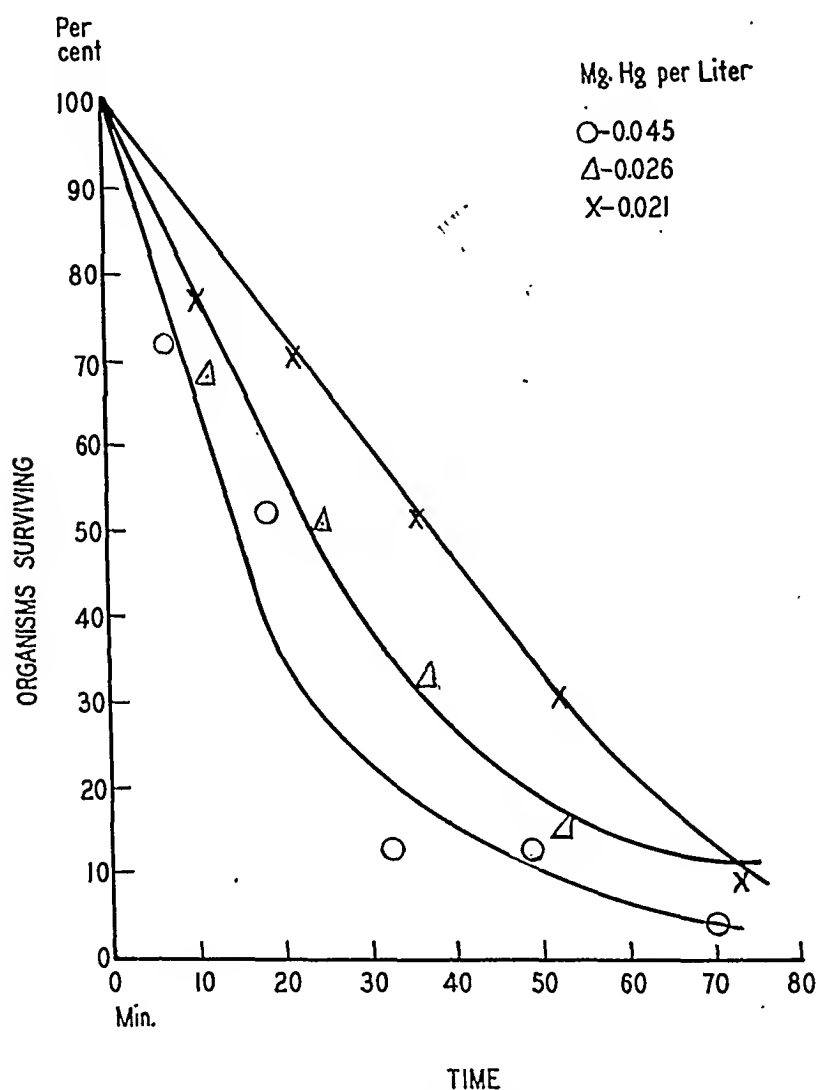


FIG. 8.—Bactericidal action of mercuric chlorid in saline.

is required to kill 50% of the standard suspension of organisms in the presence of serum than is required to kill 50% of the organisms in saline in the same time. It is evident from this that the reaction between serum and the mercurial is the faster, the serum being present in the larger amount. Whereas 0.07 mg. of Mercurial M as mercury is required to kill 50% of the suspension in saline in 20 minutes (Fig. 10), 24 mg. of Mercurial M as mercury are required

to kill the same number of organisms in the serum in the same time. Thus 24 — 0.07 mg. of Mercurial M are being inactivated for each 0.07 mg. of Mercurial M combining with the standard suspension of bacteria. About 340 molecules of Mercurial M are being inactivated by the serum for every one combining with the bacteria in this concentration of Mercurial M. All of the mercurials

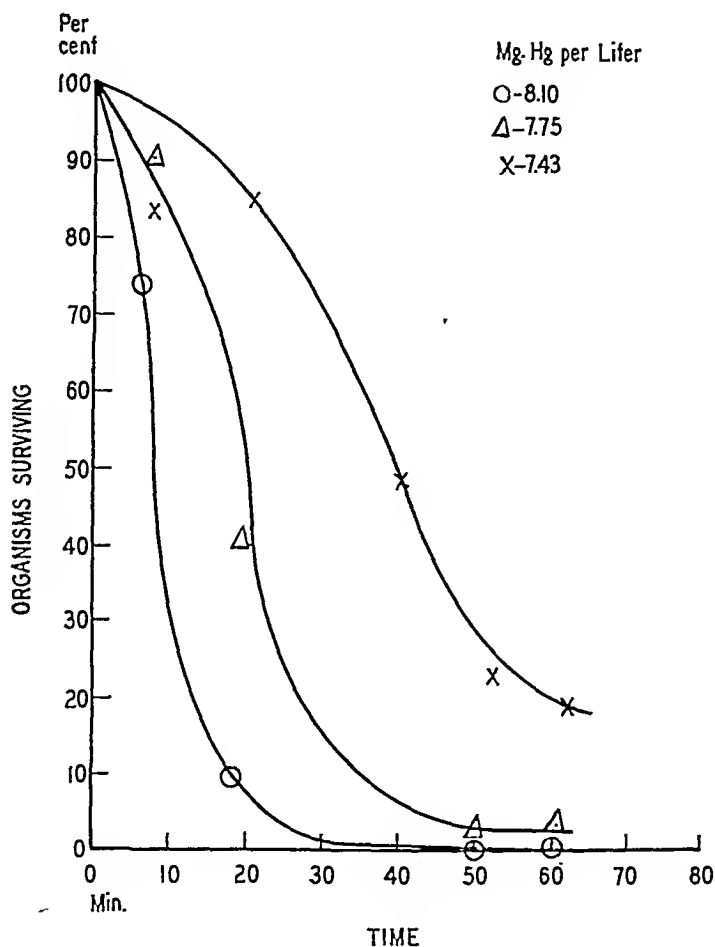


FIG. 9.—Bactericidal action of mercuric chlorid in serum.

studied show this tendency to be inactivated by serum, Mercurial M being given as an example. Where any of these mercurials is tested in the presence of a homologous immune serum, there is a still greater tendency toward inactivation of the antiseptic.

2. *The Relative Efficiency of the Mercurials Studied.* The survival level curves in serum (Fig. 11) indicate that there is a rapid falling off in the efficiency of Mercurial M with time. Thus, if

Mercurial M were to be given as an intravenous antiseptic, sufficient amounts would have to be given to exert antiseptic action in as short a time as possible, so as to get the maximum efficiency per unit of Mercurial M. The relative efficiency of these mercurials in serum or in saline for any time and concentration can be estimated by means of an equation, providing two points on the 50%

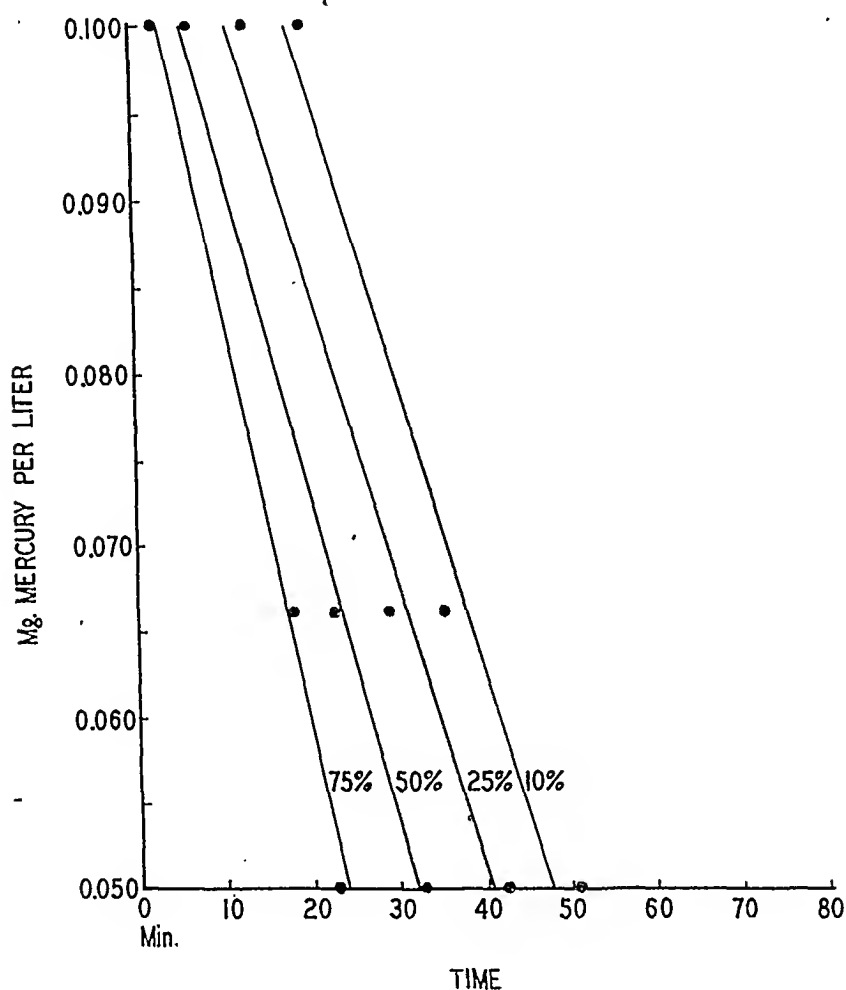


FIG. 10.—Time-concentration survival levels of a standard suspension of *E. typhosa* in mercurial M in saline.

survival level curves are known. As it has already been shown that such survival level curves are straight lines, these lines can be extended from two points to get the effect of any concentration within reasonable limits. If we let the standard efficiency of any mercurial equal 1 at that concentration on the survival level curves at which 50% of the organisms are killed in 30 minutes, then the relative efficiency of that mercurial in killing 50% of the same suspension of organisms at another concentration becomes:

$$1 \times \frac{T}{t} \times \frac{C}{c} = \text{Relative efficiency}$$

T = Standard time = 30 minutes.

t = Time required to kill 50% of the organisms at the concentration being investigated.

C = Standard concentration.

c = Concentration being investigated.

1 = Standard efficiency (unity).

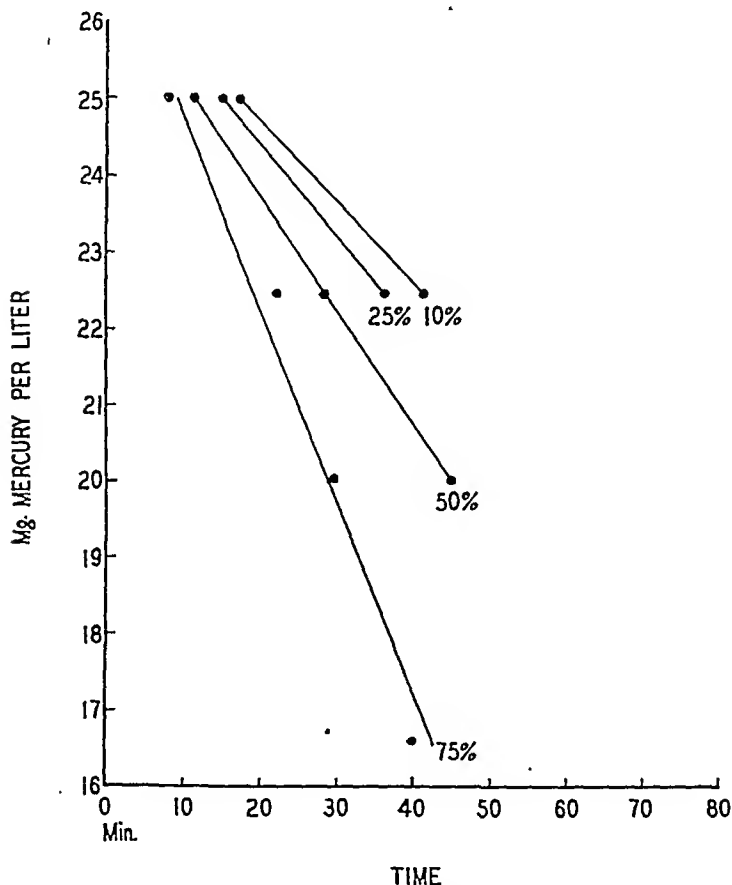


FIG. 11.—Time-concentration survival levels of a standard suspension of *E. typhosa* in mercurial M in serum.

Where the standard efficiency is unity, it must be multiplied by the standard time over the time being investigated to provide for change in efficiency due to time, and this result must be multiplied by the standard concentration over the concentration being investigated to provide for change in efficiency due to concentration. This gives the relative efficiency of the concentration being investigated as efficiency changes with time and concentration. The proportionality of the survival levels as to time and concentration are not of the first order, but of the second order, as in the following

example when the concentration of Mercurial M is slightly raised when it acts on the standard suspension of organisms in serum (Fig. 11):

$$1 \times \frac{C}{c} = \frac{22.5}{25} = .9 \quad \frac{T}{t} = \frac{30}{15}$$

$$1 \times \frac{C}{c} \times \frac{T}{t} = .9 \times \frac{30}{15} = 1.8$$

Thus raising the concentration of Mercurial M one-ninth when it acts on bacteria in serum at the 50% survival level, increases its efficiency almost twice. The other mercurials increase in efficiency with concentration.

Similar survival level curves have been prepared for the other antiseptics studied, and their efficiency can be compared with that of Mercurial M by an inspection of Table 1. Table 1 shows the

TABLE 1.—RATIO OF COMBINATION OF MERCURIALS WITH BACTERIA AND WITH SERUM IN MILLIGRAMS OF MERCURY PER LITER.

Mercurial.	1. With bacteria, mg. Hg.	2. With serum, mg. Hg.	3. Ratio of combination.
Merthiolate	0.0062	87	14,000
Mercurochrome	0.1340	110	800
Mercurial M	0.0530	22	410
Mercuric chlorid	0.0160	7.6	300

amounts of mercurials, as mercury, necessary to kill 50% of the standard suspensions of organisms used in 30 minutes. The data in this table have been derived from the survival level curves.

The figures in Column 1, Table 1, represent the amount of mercurial as mercury necessary to kill 50% of the standard suspension of organisms in 30 minutes. Column 2 represents the amount of mercurial, as mercury, necessary to accomplish the same degree of killing in the same time, in the presence of 80% serum. As has already been shown, the figures representing the reaction of the mercurials with bacteria in serum represent the sum of two distinct reactions of the first order, represented by the equation:

$$A + B + C = AC + AB + C + B$$

where $B + C$ equals unity, and where A represents a quantity of mercurial, and B and C represent bacteria and serum respectively. The figures in Column 1, Table 1, represent AB of the equation, whereas the amount of mercurial combined with bacteria and serum is represented by $AB + AC$. Therefore, the quantity of mercurial combined with the serum proteins is the quantity AC . By subtracting AB from $AB + AC$, or the figures in Column 1 from the figures in Column 2, we obtain the exact figure for the amount of mercurial combined with the serum proteins. This gives us a basis for determining the ratio of the amount of mercurial combined with bacteria and the amount combined with the serum proteins,

represented by AC/AB. These ratios are given in Column 3, Table 1. It at first appears that Merthiolate is the best antiseptic studied, as only 0.0062 mg. of Merthiolate, as mercuric, is required to kill 50% of the standard suspension of organisms, whereas larger amounts of the other three mercurials are required. The efficiency of Merthiolate, when used in amounts great enough to kill all of the standard suspension of organisms is very poor. When used in the presence of 80% serum, its efficiency is reduced 14,000 times as 87 mg. of this antiseptic, as mercuric, combine with 1 liter of normal horse serum in 30 minutes, with a beginning concentration great enough to kill 50% of the standard suspension in 30 minutes. The ratios in Table 1 then represent the number of molecules of mercurial inactivated by the serum proteins for each single molecule used in killing the bacteria. The difference in ratio for the different mercurials can be attributed to their different reaction rates, of which the ratio is a measure. Thus, even though Merthiolate has a rapid reaction rate, and therefore appears to be a useful antiseptic in saline, this same rapid reactivity in the presence of serum makes its inactivation by the serum proteins very rapid. As the greater portion of the mercurial combines with the serum, as evidenced by the ratios (Table 1), these ratios then become a measurement of the efficiency in serum of the antiseptics studied; the ratio is an inverse function of the efficiency in serum.

3. *The Mercurials as Intravenous Antiseptics.* As the mercurials were considered for intravenous antiseptic, the total amount necessary to kill the organisms becomes of importance. It is evident from Table 1 that mercuric chlorid, from this viewpoint, is the least bad of the four antiseptics studied, as less of it is required than of the others to kill 50% of the standard suspension in serum under standard conditions, and its ratio of inactivation is among the lowest of the four mercurials studied. These ratios of inactivation must be taken into consideration, as they depend upon time and concentration, and therefore upon the efficiency of the mercurials studied.

It has also been noted that Merthiolate has a tendency to decompose with time, even in the dry state, with a subsequent loss of bactericidal activity, in saline or serum.

4. *Purified Mercury-Protein Compounds.* By a series of chemical experiments, it has been possible to determine the maximum combining power of serum with the mercurials studied. The maximum quantity of either mercurial which might combine with serum was estimated from the plating experiments. A quantity of each mercurial in excess of this amount was added to four separate 1-liter amounts of normal horse serum. The mixtures were allowed to stand 24 hours, as maximum combination takes place in this time. The excess mercurial was removed by means of electro-ultrafiltration as described by Czarnetzky.³ By means of this procedure, all

particles of smaller dimensions than protein molecules were removed. Electro-ultrafiltration was considered to be complete when the ultrafiltrate was free of mercury and no longer bactericidal. The mercury-protein compounds were then analyzed for mercury by a modified Pregl electro-deposition method. In this method the mercury-protein compound is first digested with fuming nitric acid and Superoxyl in a wet combustion, and then placed in a glass vessel containing a weighed solid gold cathode, and a platinum anode. A current of 3.5 volts is applied for 1 hour at 50° C. The temperature is then lowered to near 0° C. The gold cathode is removed while the current is still being applied, dried, and weighed.

5. The *Maximum Combining Power of Serum Proteins with Mercury*. In Table 2 the maximum amount of mercurial, as mercury, combined with 1 liter of normal horse serum is given.

TABLE 2.—MAXIMUM AMOUNT OF MERCURIAL COMBINING WITH 1 LITER OF NORMAL HORSE SERUM IN GRAMS OF MERCURY PER LITER.

Mercurial.	Mercury combined.
Merthiolate	0.39
Mercurochrome	0.29
Mercurial M	0.35
Mercuric chlorid	0.29

Each of the mercurials combines with serum to about the same extent; approximately 0.35 gm., as mercury, per liter.

6. *Bactericidal Power of Mercury-Protein Compounds*. Strangely enough, not only are these mercury-protein compounds not bactericidal in the slightest degree, but bacteria grow readily in solutions of these compounds. This is an indication that all of the mercury present is bound by the protein. These compounds are also hydrolyzed by trypsin, as indicated by the formol titration. In these compounds only the mercury portion of the antiseptic molecule is bound to the proteins. The other portion of the antiseptic molecule is present almost entirely in the ultrafiltrate. Portions of these compounds containing approximately 0.35 gm. of mercury per liter were adjusted to pH 7.0 and then were plated with equal volumes of the standard suspension of organisms used, after allowing the mixtures to stand for 1 hour. Table 3 gives the results of such plating experiments.

TABLE 3.—BACTERICIDAL ACTION OF PURIFIED MERCURY-PROTEIN COMPOUNDS (MAXIMUM NON-POLAR COMBINATION).

Protein-mercury compound.	Dilution.	Effect.
Mercurial M	1:1	No killing
Mercurochrome	1:1	No killing
Merthiolate	1:1	No killing
Mercuric chlorid	1:1	No killing

It is obvious that protein-mercury compounds containing no unbound mercury are not bactericidal. They are not even bacterio-

static. We have observed growth of *E. typhosa* in them after 48 hours' incubation at 37° C.

7. *Mixtures of Serum and Mercurials.* On the basis of the quantities given in Table 2, amounts of each of the mercurials 10% less than the amounts combined with 1 liter of normal horse serum were added to other 1-liter lots of the same serum. These mixtures were allowed to stand 24 hours.

It was found that these mixtures exerted very little antiseptic action, as the mercury was combined with the proteins in a true non-polar stoichiometrical combination. When serial dilutions were made and plated with the standard suspension of organisms, the amount of antiseptic activity possessed by the serum-mercurial mixtures was found to be very slight, even after 1 hour of contact with the organisms. This can be seen in Table 4. As all components

TABLE 4.—BACTERICIDAL ACTION OF MIXTURES OF MERCURIALS AND SERUM ON *E. typhosa*.

Dilution of mixture.	1:1.	1:4.	1:8.	1:16.	1:20.	1:200.
Mercurial M	0	0	0	x	x	x
Mercurochrome	0	0	x	x	x	x
Merthiolate	0	0	x	x	x	x
Mercuric chloride	0	0	0	x	x	x

0 indicates no growth. x indicates growth.

of the antiseptic molecules were present in these mixtures, it can be concluded that these antiseptics exert their action on bacteria almost wholly by virtue of their mercury content.

When normal horse serum is dialyzed, the dialysate has a very slight inactivating action, demonstrable only against very dilute solutions of mercurials. This is probably due to such actively reducing substances as cysteine. Plating experiments show that traces of cysteine abolish the bactericidal action of dilute solutions of Mercurial M in saline.

Experiments are in progress designed to identify those groups in serum proteins which are responsible for the inactivation of mercurials.

Discussion. Kobert⁴ gives 180 mg. of mercuric chloride as the lethal dose by oral administration. The maximum amount of mercury, in the form of any of the mercurials studied, that can combine with the blood serum of an average patient is approximately 1 gm., assuming the serum volume to be 2½ liters. This leaves out of consideration the fibrinogen, tissue proteins, intima of the bloodvessels, blood corpuscles, and so forth. The figure of 1 gm. for the total combining capacity of the proteins with which intravenous mercurials come into contact is therefore a minimum.

From the plating experiments it would take at the very least 250 mg. of Mercurial M, acting in 30 minutes, to kill one-half of the organisms in the blood stream of the average patient, with no margin of safety for the combination with other body proteins.

This figure is again beyond the lethal dose of mercury, and obviously these mercurials cannot be used successfully as intravenous antiseptics.

It is evident that any antiseptic to be suitable for intravenous therapy must combine with bacteria and serum in a ratio favorable to its combination with bacteria. The ratio of the combination of the mercurials which have been investigated is too greatly in favor of the proteins, with the result that they cannot be used successfully in the blood stream. It is suggested that this criterion will be a useful guide to the chemist in the search for suitable intravenous antiseptics.

These mercurials combine with serum proteins to the same degree, but at different rates. As all the experiments were carried out at 22° C., these rates would be approximately twice as great at body temperatures, favoring more rapid combination with the serum proteins. Nevertheless, in a relatively short time interval, it would seem that their fate in the animal body must be much the same. Mercury-protein compounds are very stable, as they are not broken down by the passage of a direct 110 v. current either in dilute or concentrated solutions. Therefore it would seem that the toxicity of these mercurials, when injected intravenously, except for a very few moments after injection, must be overwhelmingly the toxicity of their compounds with serum proteins. Thus unless used in large amounts, it is the mercury-protein compounds which come into contact with tissue cells and enzymes. This might well be taken into account in studies of their effect on tissue cultures,⁵ or enzymes. Macht⁶ found that mereurochrome was less toxic to oxidase of muscle than mercuric chloride, but when one converts his figures to concentration in terms of mercury, both mereurochrome and mercuric chloride have about the same effect. Kolmer and Lucké⁷ found that the degree of tissue injury caused by different preparations of mercury appears to bear a direct relation to the actual amounts of pure mercury absorbed irrespective of the kind of preparation and route of administration. Birkhaug¹ also warned against the synergistic effect of the toxins of streptococci and mercurials on the kidney.

Summary. 1. The efficacy of certain mercurial antiseptics has been determined in saline and in serum, and survival level curves for the activity of Mercurial M on *E. typhosa* have been analyzed.

2. The activity of a mercurial antiseptic in serum is reduced to 0.33%—0.007% of its activity in saline.

3. The killing power per unit weight of mercury of all these mercurials falls off rapidly with dilution when used in the presence of serum.

4. Mercurial antiseptics exert their action almost wholly in virtue of their mercury content.

5. Analysis shows that 0.29 to 0.39 gm. of mercury is bound

irreversibly per liter of serum by the proteins in a mixture of serum and an excess of any of the mercurials studied. Hence the maximum non-polar combining capacity for serum of the mercurials studied is about the same.

6. The inhibiting effect of serum on mercurials is caused by the fact that the non-polar compounds of serum and mercury are not merely less bactericidal but are completely devoid of bactericidal action. Any killing may be attributed to unbound mercury present in excess.

7. It has been found that Mercurochrome, Merthiolate, Mercurial M, and Metaphen, like mercuric chlorid, are unsuitable for intravenous antiseptics, as they combine with the serum proteins so rapidly that they are almost wholly inactivated. This, of course, does not apply to disinfection of the skin—a subject outside the scope of this paper.

8. Amounts of any of the mercurials studied sufficient to sterilize the blood stream are many times the lethal dose.

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STUDIES ON TRANSIENT VENTRICULAR FIBRILLATION.

IV. OBSERVATIONS ON THE CLINICAL AND GRAPHIC MANIFESTATIONS FOLLOWING THE REVIVAL OF THE HEART FROM TRANSIENT VENTRICULAR FIBRILLATION.

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THESE studies are concerned with the cardiac mechanism following the spontaneous revival of the heart and the clinical manifestations which occurred simultaneously in 7 patients who have experienced transient seizures of ventricular fibrillation during the presence of

transient or established *A-V* dissociation. They are based on correlated observations obtained while the patients were in the electrocardiographic circuit and may be best appreciated from descriptions of several such episodes.

On one occasion, observations were made during and subsequent to a Stokes-Adams seizure with convulsive movements which lasted approximately $3\frac{1}{2}$ minutes (Fig. A-1 and 2). The ventricular oscillations during syncope were almost uniform in shape and size and averaged 300 per minute (Fig. A-1A) until shortly before the revival of the heart when they decreased in amplitude and became irregular and of lower voltage, although of the same duration (Fig. A-2A). This transient period of ventricular fibrillation ended with a postundulatory pause (Fig. A-2B) which measured 0.56 second and was followed by complete standstill of the ventricles for a period of 13 seconds (Figs. A-2B to C).

The ventricular rhythm following this interval was initiated by a ventricular complex which was totally different from the others that followed it (Fig. A-2D). The second ventricular beat in this period of revival followed the first at an interval of $1\frac{1}{2}$ seconds (R2, Fig. A-2E). This was in turn succeeded by a series of similar ventricular complexes which accelerated the ventricular rate progressively until it averaged 71.4 beats per minute within 2 minutes after the spontaneous revival of the heart (Fig. A-2F; Fig. B-1).

Five minutes later the ventricular rate slowed to 38.4 beats per minute and now the main ventricular deflections were at times wider and of higher voltage, but upright in form (Fig. B-2). The rate of the ventricles gradually increased again to 75 beats per minute and the deflections began to change their direction so that sometimes they were downward whereas hitherto they had been upward (Fig. B-3).

Within the next 5 to 10 minutes the ventricular rate was further increased from 75 beats per minute to 88.2 beats (Fig. B-4), and the main ventricular deflections now reverted from an upward direction to a downward one. They increased in height and measured 10 mm. Suddenly and abruptly the heart rate became accelerated to 150 beats per minute (Fig. B-5) and remained so for almost 7 minutes before it slowed to a level of 49.3 beats (Fig. B-7). Finally there was a gradual return to the original inherent ventricular rate and rhythm $4\frac{1}{2}$ hours after the onset of the seizure of transient ventricular fibrillation.

In the meantime the auricles at first beat regularly during the standstill of the ventricles but for a short period they also slowed progressively for a few beats (Fig. A-2B, C). There then ensued a waxing and waning of their rate (Fig. B-1, 2) in which they kept pace with the ventricles until they suddenly began to fibrillate (Fig. 2-3A). The auricular fibrillation persisted even during the period of tachycardia so that the two irregularities existed simulta-

neously, but they were independent of each other and one rhythm did not apparently influence the other since complete auriculoventricular dissociation was present all the time.

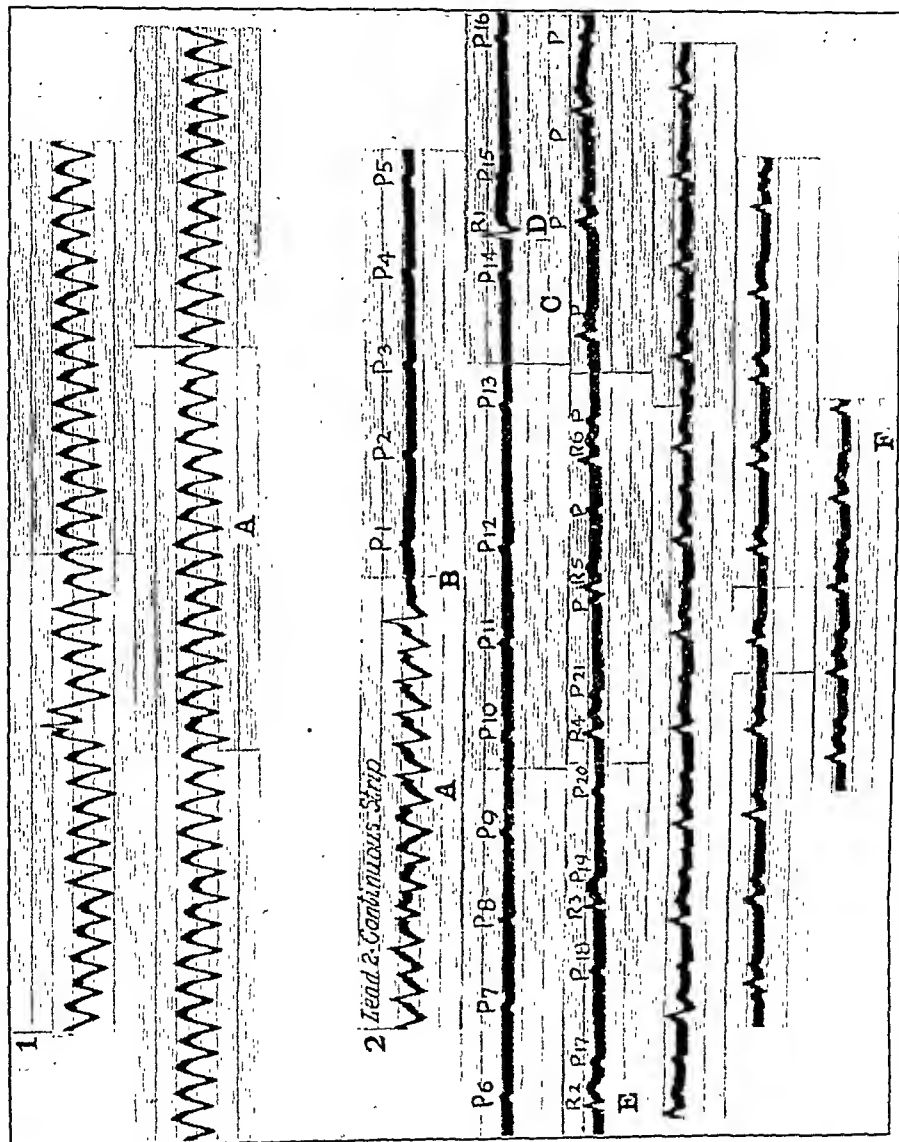


FIG. A-1.—An electrocardiogram obtained during syncope. FIG. A-2. Later records showing a period of ventricular fibrillation ended by a postsynclatory pause and followed by standstill of the ventricles (B-C). This in turn is followed by a progressive increase in the ventricular rate (D-F).

During the stage of tachycardia, periodic variations in the ventricular complexes were noted (Fig. B-5A, B and 6A, B, C) which came at regular intervals, at first every tenth ventricular beat being interrupted by a variable complex, and then only every eighth beat until the heart rate returned to an average of 48.3 beats.

In this entire period the patient was in a state of stupor but could be easily aroused, although when spoken to she was very confused and did not regain full control of her senses until 5 hours had elapsed from the onset of the major syncopal attack that preceded these irregularities.

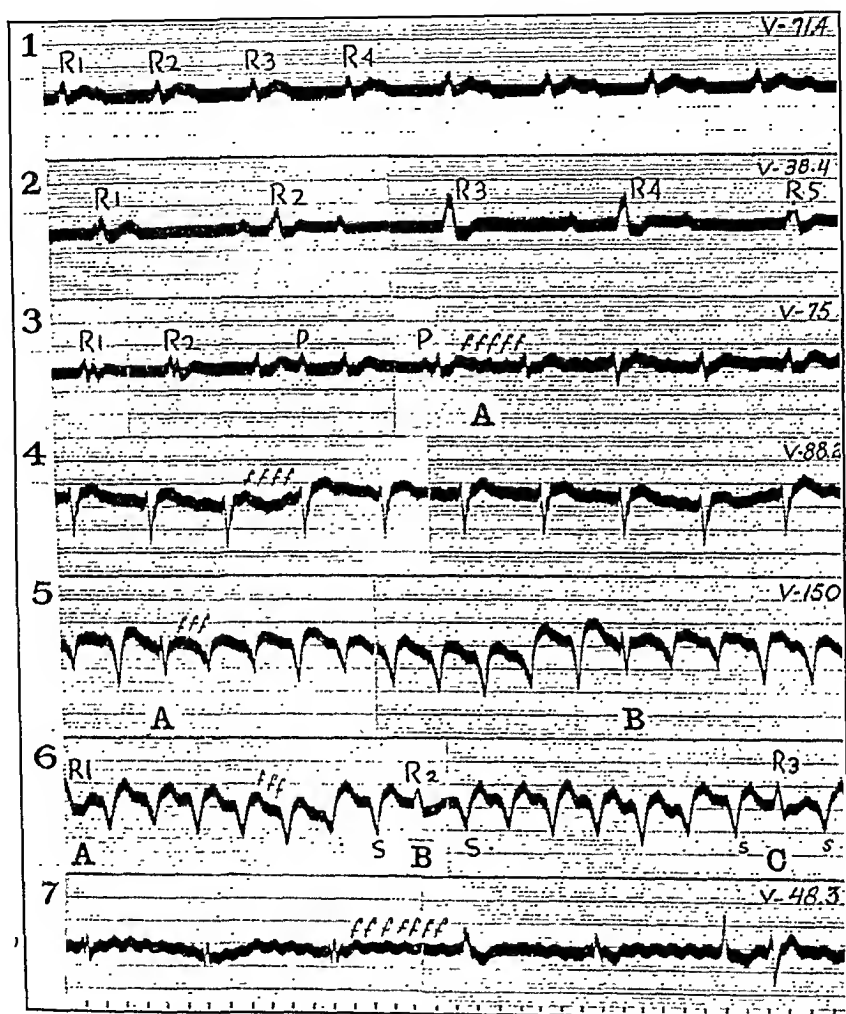


FIG. B-1.—Electrocardiograms obtained on the same patient as in Fig. A 2 minutes after the spontaneous revival of the heart. The ventricular rate now averages 71.4 beats per minute. FIG. B-2. The electrocardiogram obtained 5 minutes later. The ventricular rate has slowed to 38.4 beats per minute. FIG. B-3. Within the next 5 minutes the ventricles reached 75 beats per minute and the auricles began to fibrillate. FIG. B-4. A few minutes later the ventricular rate was 88.2 beats per minute. Note the change in direction of the main ventricular deflections. FIGS. B-5 and B-6. Now the ventricles are abruptly accelerated to 150 beats per minute and remain so for 7 minutes. FIG. B-7. The return to the basic rhythm 4½ hours after the onset of ventricular fibrillation.

The electrocardiograms of another postfibrillatory period were obtained from the same patient as the above following a seizure of transient ventricular fibrillation lasting about 4 minutes. This

long seizure of unconsciousness with epileptiform convulsions ended in apnea and the patient appeared to be dead since no heart sounds were audible and no pulsations of any peripheral vessels were visible

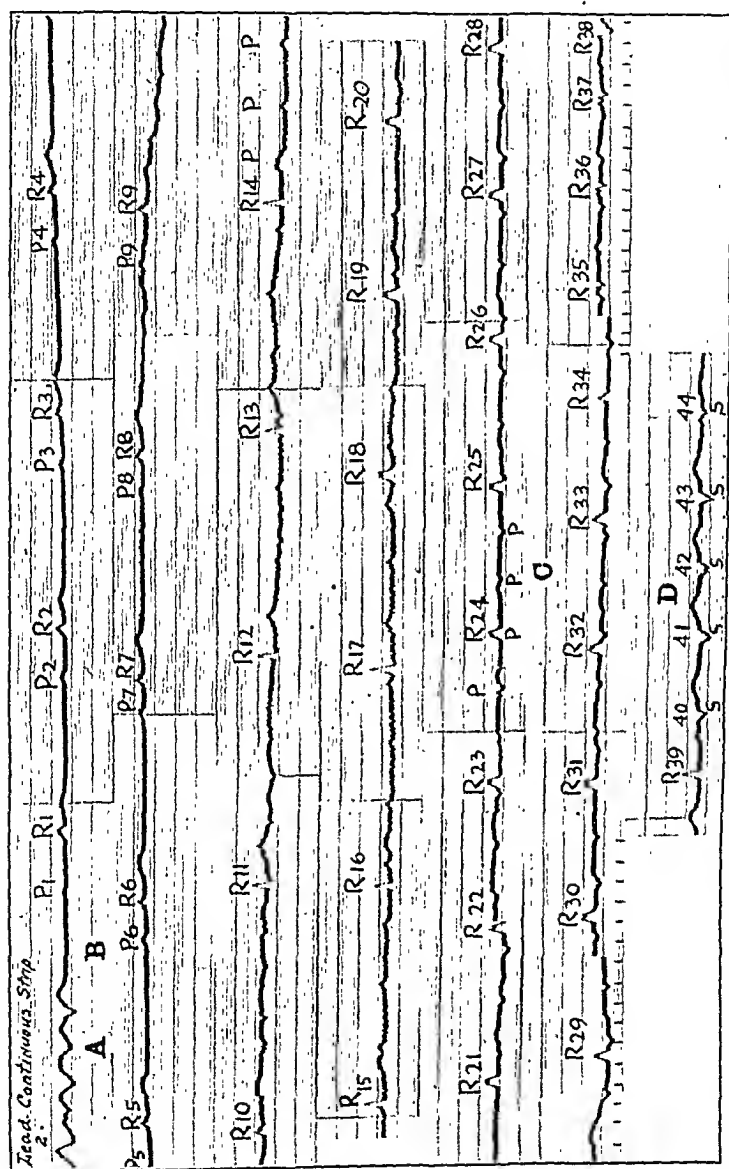


FIG. C.—An electrocardiogram showing the progressive increase in the ventricular rate following the spontaneous revival of the heart from ventricular fibrillation. Note that the auricular rate keeps pace with the ventricular rate and reaches 115 beats per minute.

or palpable. There was patchy cyanosis with lividity of the entire body as is seen in individuals postmortem. Suddenly a very faint beat could be heard at the apical region of the heart and this coincided with the appearance of a very weak pulsation at the wrist.

Exactly 2 seconds later a forceful apical beat coincided with a flushing of the face and a disappearance of the cyanosis. The patient opened her eyes $1\frac{1}{2}$ minutes later, looked vaguely around

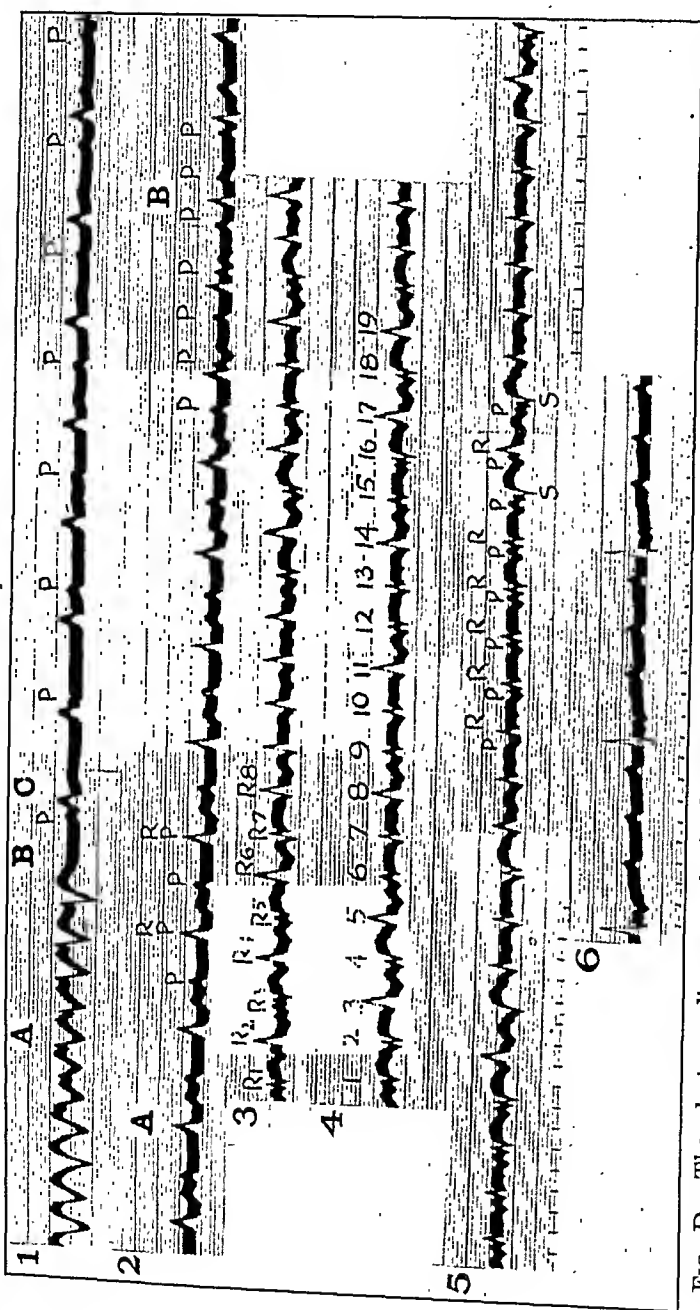


FIG. D.—The electrocardiograms obtained following the spontaneous revival of the heart from ventricular fibrillation, showing a ventricular rate of 71 beats per minute (Fig. D-1); increasing within the next 3 minutes to 77 beats per minute (Fig. D-2); suddenly accelerated to 160 beats per minute (Fig. D-3); with a final return to the basic ventricular rate of 36 beats per minute (Fig. D-6), $\frac{1}{4}$ hour after revival of the heart.

in a semistuporous condition, uttered some unintelligible words and finally lifted her head at an angle and screamed very loudly, unconscious of what she was doing. Within 2 minutes she was oriented, recognized the physicians at

the bedside and apologized for having soiled the linen since she was always incontinent of urine and of feces during her syncopal attacks.

The ventricular oscillations during this syncopal attack were wide, each measuring almost $\frac{2}{5}$ second (Fig. C-A) and spontaneous revival

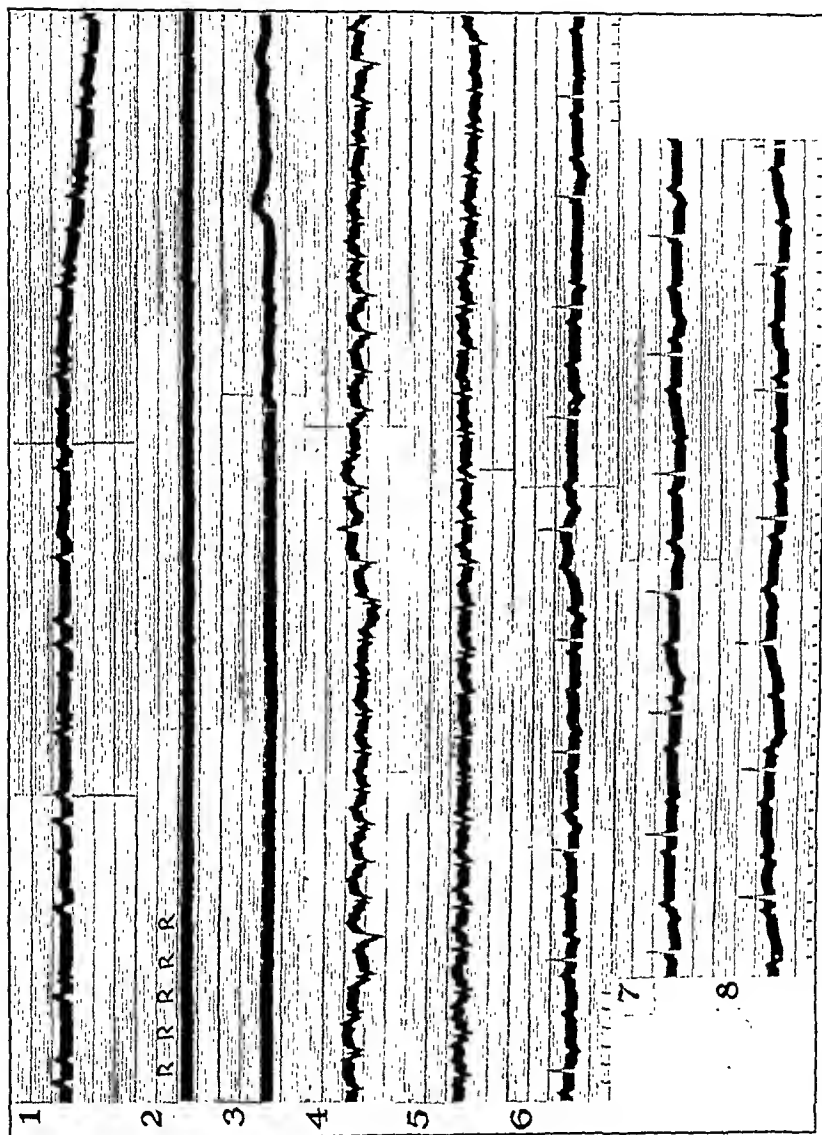


FIG. E.—The electrocardiogram showing the revival of the heart from ventricular fibrillation in a patient in whom there was a marked depression of the electrical deflections in which the ventricular complexes are barely visible (Fig. E-2 and 3). No heart sounds were audible during this period. The pulses were not palpable.

of the heart was preceded by a postundulatory pause of 1 second's duration (Fig. C-B) and was ushered in by an intermediary idio-ventricular rhythm with a ventricular rate averaging 24 beats per minute. An auricular complex preceded each of the first 14 ven-

tricular deflections of this intermediary idioventricular rhythm. It is questionable, however, whether there was any relationship between these auricular beats and their successive ventricular complexes, for in the early portions of this record the interventricular periods as well as the interauricular periods were constantly variable. The auricles, nevertheless, kept pace with the ventricles until the auricular rate suddenly increased to 115 beats per minute and remained so until the return of the inherent ventricular rhythm. Some of the auricular complexes became inverted after their rate had accelerated (Fig. C-D).

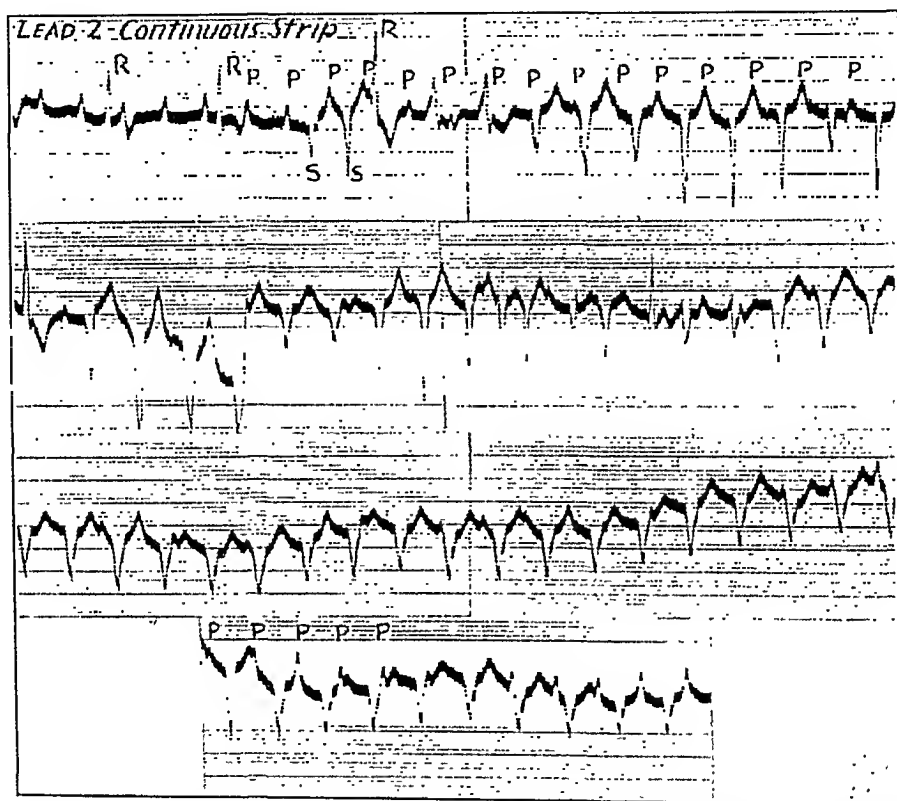


FIG. F.—Electrocardiograms showing a postfibrillatory tachysystole in which there is a sudden acceleration of the ventricles after the establishment of the basic rhythm. Such mechanisms usually heralded another seizure of ventricular fibrillation.

As the rate of the heart chambers increased progressively, the ventricular complexes also changed, reverting from a dextrogram to a levogram when they assumed a rate of 75 beats per minute (Fig. C-D).

Again, electrocardiograms were obtained from the same patient as the above at the end of a day when she was having as many as 100 syncopal attacks during a period of 12 hours. At such times when one attack appeared after another, she was completely disoriented. She moaned all the time. Her respirations were labored

and irregular. Sometimes her expirations were very short and at other times they were prolonged. She was constantly wet from incontinence of urine and she vomited all nourishment, including fluids.

An interesting phenomenon noted was that even when she had stopped having these syncopal attacks and she had regained full consciousness, the control of her urinary bladder was totally lost. Now she was incontinent all the time and this incontinence lasted for a period of 48 hours when she gradually began to regain control. Incidentally, whereas hitherto she had been free from edema, now after these repeated attacks over a very short time, her face became bloated, her eyes were puffy, and all of her extremities were markedly swollen.

Similar observations on another patient were obtained after a Stokes-Adams seizure lasting a little over 3 minutes. The attack was associated with ventricular oscillations that were wide and aberrant but almost uniform in height, averaging 187 beats per minute (Fig. D-A). This seizure ended with a postundulatory pause (Fig. D-1B) and was followed by an idioventricular rhythm averaging 71 beats per minute (Fig. D-1C). Consciousness was, however, not restored during this period and with the appearance of this intermediary idioventricular rhythm, Cheyne-Stokes respirations set in and lasted for the ensuing hour.

The auricles averaged 53 beats per minute and increased in rate very gradually until within 3 minutes after the revival of the heart (Fig. D-2) they averaged 77.3 beats. The ventricular complexes during the superimposition of an auricular beat were of a different form from those that did not coincide with the *P* wave. The former were larger and more aberrant (compare Fig. D-2A and 2B).

Suddenly and very abruptly, the ventricular rate accelerated to 166 beats per minute, the auricles in the meantime keeping pace with them. Of interest in these records (Fig. D-3, 4, 5) are the variable ventricular complexes that at times alternate at every second beat and sometimes at every fourth beat. Frequently the intervals between periods of alternation were greater (Fig. D-5). The auricular complexes are clearly distinguished when this tachysystole is lowered to 150 beats per minute (Fig. D-5). When the inherent idioventricular rhythm returned to a rate of 36 beats per minute, then the auricles remained at their former rate of 136 beats for some time before they slowed to their usual average of 100 beats.

This entire postfibrillatory period lasted almost $\frac{1}{2}$ hour. Similar electrocardiograms were obtained repeatedly in 5 other patients with either transient or established auriculoventricular dissociation.

In the same patient another type of cardiac mechanism was encountered at a time when the major syncopal seizure of the day was followed at first by an intermediary idioventricular rhythm

with a regular rate averaging 71 beats per minute, $2\frac{1}{2}$ minutes after the spontaneous revival of the heart (Fig. E-1).

Despite the revival of the heart, however, the patient screamed after the first few effectual beats of the heart appeared and then lapsed into coma. A period of quiescence ensued with a very marked depression in the voltage of all the complexes (Fig. E-2, 3) which could barely be distinguished, although on careful examination there is a regular periodicity in the small wavelets that are visible, their rate being 166 beats per minute.

This type of mechanism continued for only 68 seconds before it was replaced by a deflection with increased voltage resembling other records encountered previously. Compare Fig. E-4 and 5 with Fig. D-3 and 4. During these abnormal increases in the ventricular rate, the auricles beat independently of the ventricles, although the auricular rate kept pace with the ventricles.

Within 28 minutes after its onset, the postfibrillatory period slowed to a ventricular rate of 60 beats per minute (Fig. E-6) and finally 12 minutes later it resumed its level previous to that of the onset of syncope, which was 46.8 beats per minute (Fig. E-8) and remained so for the rest of the day. Cheyne-Stokes respirations which set in soon after the onset of this cardiac mechanism disappeared within 1 hour.

On several occasions it was noted that when the inherent rhythm was reestablished very soon (within 15 to 45 seconds) after a syncopal seizure, due to ventricular fibrillation, there elapsed a few minutes, during which time the ventricles beat, slowly at first, but regularly, at a rate averaging 60 beats per minute (Fig. F-A), while the auricles averaged 187 beats. Suddenly and abruptly (Fig. F-B) the ventricles would start beating at 150 per minute and the auricles would slow to the same rate and keep pace with the ventricles for a time before either one of two conditions resulted. Sometimes the tachysystole would slow abruptly or gradually to the originally established rhythm of the ventricles during auriculoventricular dissociation or else the tachysystole would be part of the premonitory period of another seizure of transient ventricular fibrillation.

These postfibrillatory tachycardias of the ventricles were unusual in that the auricular complexes could readily be made out during the presence of aberrant ventricular complexes even though there was a waxing and waning of the ventricular rate at such times. There was a very marked variability in the size, shape, and form of the ventricular deflections comprising this increased postfibrillatory period and there is every likelihood that most of the beats originated below the bifurcations of the auriculoventricular node either in one bundle or the other.

Discussion. These observations indicate that the successive events following the spontaneous recovery of the heart after transient ventricular fibrillation are of a very distinct nature. If the

periods of ventricular fibrillation were of short duration (not greater than 50 seconds) then revival of the heart was immediately associated with the previously established inherent rhythm of the ventricles. If fibrillation was of longer duration, however, or if repeated shorter attacks preceded one single long seizure, then the successive events leading to recovery of the heart from fibrillation were more variable.

Sometime a postundulatory pause ended the transient period of ventricular fibrillation and was followed by standstill of the ventricles. This occurred both when the inherent rhythm of the ventricles alternated with the normal sinus rhythm so as to produce interference with dissociation or when there was established auriculo-ventricular dissociation. The postfibrillatory standstill of the ventricles varied in duration but the average of all the recorded standstill periods was $23\frac{1}{2}$ seconds. Again, instead of complete standstill of the ventricles (Fig. A-2) there occurred an irregular slowing of the ventricles in which the longest ventricular cycle appeared sometime after the recovery of the heart (Fig. C). Occasionally a period of slowing of the inherent rate of the ventricles appeared several minutes after the postfibrillatory standstill but was preceded by a moderate increase in the rate prior to this (compare the ventricular rate in Fig. A-2B to F with Fig. B-1 and 2).

It is of some interest to speculate on the reasons for the variable change in the heart rhythm observed in the immediate revival of the heart following ventricular fibrillation. It is well known since Gaskell's¹ experiments on the cold-blooded heart that the rapidity with which an idioventricular rhythm develops depends in part upon the rate at which the ventricles beat previously. In studying the behavior of the ventricles when they were dissociated from the auricles in complete heart block, Erlanger and Hirschfelder² observed that when an idioventricular rhythm of the isolated ventricles was increased by the application of electrical shocks, cessation of stimulation was followed by a period of slow contraction of the ventricle. The duration of the "stoppage of the ventricles" was found to depend largely upon the rate and duration of the preceding period of artificial stimulation and upon a certain "depressed" condition of the heart at the time of stimulation. These observations were subsequently confirmed by Cushny³ and attributed by him, in addition to the rate and duration of stimulation, to a reduction of oxygen in the perfusing fluid resulting in *asphyxia*, as well as to a diminution of the perfusing fluid at such times.

Both Erlanger and Hirschfelder, and Cushny noted that there were two types of stoppages of the ventricles following artificial stimulation. In the first type, the first ventricular cycle after cessation of stimulation appeared to be the longest and in the other type the successive ventricular cycles increased in length from beat to beat for several beats before there appeared gradual acceleration

of the ventricles to their return to the inherent rhythm. In none of their experiments was the ventricular rate after the period of standstill of the ventricles found to be greater than the inherent basic rate after the establishment of auriculoventricular dissociation.

They further observed that the slowing and the pauses after cessation of artificial stimulation were generally more marked and more persistent in the latter phases than in the beginning of the experiments. As the "energy" of the heart decreased, the results of the accelerated rhythm became greater and a longer interval had to be allowed to obtain the return of the rhythm prevailing before the interference. Spontaneous acceleration of the ventricles were similarly observed to result in periods of slow ventricular rhythm. Cushny concluded that this low phase was not inhibitory in the origin since it occurred after full atropinization of the animal as well as before. He felt the phenomenon was due to a depression of the function of stimulus formation in the ventricular pacemaker which presents analogy to the fatigue of striated muscle and that the contractility and excitability of the ventricles was not diminished at such times.

It would appear that the cardiac mechanisms observed in the postfibrillatory period in man are an almost exact parallel to the experimental studies cited above. It is conceivable that the repeated spontaneous accelerations of the heart which take place in human beings prior to and during transient ventricular fibrillation, progressively augment the fatigue of the ventricular pacemaker so as to depress its function and thus result in stoppage of the ventricles.

Since standstill of the ventricles after transient ventricular fibrillation is a natural phenomenon and is directly related to the immediate previous alteration in the rhythm of the heart, it is a fallacy to assume that the administration of any drug during a period of such postfibrillatory standstill is responsible for the revival of the heart. This was suspected by Levine and Matton⁴ in 1 of their patients with transient ventricular fibrillation in whom standstill of the ventricles was followed by revival of the heart after the intracardiac administration of adrenalin. As a matter of fact, as we have pointed out elsewhere, adrenalin in any form is contraindicated in patients who are subject to transient seizures of ventricular fibrillation for in such patients the drug precipitates and may perpetuate the fibrillary process.⁵

The Behavior of the Auricles in the Postfibrillatory Period. It has been pointed out that the auricular rate and rhythm are, as a rule, undisturbed during short runs of ventricular fibrillation, although at times it is difficult to distinguish the superimposed auricular waves upon the ventricular deflections during ventricular fibrillation. During longer runs of ventricular fibrillation, the bizarre ventricular complexes obscure completely the auricular waves and we can

only assume from experimental observations that the auricles at such times may be reflexly stimulated above their basic rate by retrograde impulses from the fibrillating ventricles. Consequently, since the auricles are dissociated from the ventricles, this effect of extra stimulation upon them results in their slowing after the cessation of fibrillation of the ventricles. We then have the same variability in the rate and rhythm of the auricles in the postfibrillatory period as was described for the ventricles. These consist of variable pauses with a waxing and waning of the rate until the inherent rhythm is established again. On rare occasions the auricles may even begin to fibrillate or flutter for a short period and continue fibrillating even though the inherent rate of the ventricles has already been reestablished. Mention should be made that since the longer runs of ventricular fibrillation are invariably associated with high grades of apnea, part of this auricular and ventricular slowing may be attributed to asphyxia, an experimental phenomenon well known to produce various grades of block.⁶

The Postfibrillatory Tachycardias. The slowing of both auricular and ventricular rates after the cessation of ventricular fibrillation is usually followed at a variable interval by a progressive increase in their rates until the reestablishment of their inherent rhythms. But, as has been pointed out above, there frequently ensues after the reappearance of this inherent rate a second period of acceleration of both the auricles and the ventricles. At times, this is a gradual affair (Fig. B-3, 4, 5, 6) in which the ventricular rate is augmented by a shortening of the interventricular periods until a maximum rate of 150 to 160 beats per minute is reached. The ventricular deflections during these tachycardias are aberrant and totally different from those of the basically inherent rhythm. It is very likely that an ectopic focus within the ventricles or in one of the bundles assumes the pacemaker at such times and after persisting for a while gradually gives way to the inherent rhythm of the ventricles.

Occasionally an ectopic focus within the ventricles may suddenly disrupt the basic rhythm (Fig. F) and initiate a tachycardia with variable ventricular complexes and an irregular ventricular rate, during which the auricles keep pace with the ventricles. The return to the inherent rhythm of both the auricles and ventricles in these instances has been observed to be gradual.

More often, this second period of acceleration of the ventricles may be associated with a bidirectional type of tachycardia (Fig. D-3) with ventricular complexes that alternate periodically at various intervals (Fig. D-4).

It was following the repeated presence of such tachycardias of the heart over several days at a time, after innumerable recurrent seizures of transient ventricular fibrillation, that these patients

invariably developed signs of severe congestive heart failure, whereas throughout their entire period of freedom from Stokes-Adams seizures, they never showed any such signs.

Summary and Conclusions. 1. Correlated observations were made of the clinical and graphic manifestations following the spontaneous revival of the heart from transient ventricular fibrillation in 7 patients with either transient or established *A-V* dissociation.

2. It was determined that revival of the heart from transient ventricular fibrillation in man is associated usually with a post-fibrillatory pause, followed by a variable standstill of the ventricles and an intermediary idioventricular rhythm with a progressive increase in the heart rate to as high as 160 beats per minute before the restoration of the basic ventricular rhythm.

3. The duration of this postfibrillatory period is dependent upon the duration of the antecedent period of ventricular fibrillation and is independent of the type of ventricular oscillations present during the fibrillatory period. It may vary from a few seconds to as long as $\frac{1}{2}$ hour at one time.

4. The spontaneous revival of the heart from transient ventricular fibrillation is associated clinically with a sudden flushing of the face and entire skin by a pink-red coloration, a forceful pulsation of the heart against the chest wall and with a barely perceptible beat of the pulse at the wrist. With these events the eyes open and loud screaming may be followed by incoherent and unintelligible speech, a very cloudy sensorium and a progressive increase in the heart rate as noted from the electrocardiograms. This in turn is followed by a progressive lowering of the heart rate again to the original basic level prior to that present before the onset of ventricular fibrillation. Coma and a period of unconsciousness may then supervene and last as long as 5 hours after a major syncopal attack.

5. The period of apnea present during ventricular fibrillation is replaced at first by irregular periods of respirations in which inspiration is prolonged. There may then appear typical Cheyne-Stokes respirations as well as all forms of irregular respiratory movements noted after asphyxia.

6. Occasionally after repeated attacks there is a generalized anasarca, involving the face, arms and the entire skin.

7. All of these symptoms and signs are so unique that a clinical diagnosis of transient ventricular fibrillation may be suspected in an individual with syncopal seizures if they are noted after the attack.

8. Since the natural course of the revival of the heart from transient ventricular fibrillation includes a period of acceleration of the heart following a postfibrillatory standstill of the ventricles, it is a fallacy to assume that any drug administered during the post-fibrillatory period is responsible for the successive events which appear after its use.

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RADIAL ARTERY CHANGES IN COMPARISON WITH THOSE OF THE CORONARY AND OTHER ARTERIES.

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THE purpose of this paper is to report observations on changes in the radial artery both at various age periods and as a result of sclerosis, in comparison with similar changes in the coronary and other muscular arteries from the same case. In doing this, we have taken the well-described coronary changes as a standard for comparison.

The radial artery has been especially investigated by Hallenberger,¹ Thayer and Fabyan,² Hesse³ and others. The reasons for this are pretty obvious. The taking of the pulse rate and pressure at the radial is presumably accompanied by palpation of the vessel wall in an endeavor to estimate the absence, presence and degree of arteriosclerotic change with possible inference from this as to sclerotic changes elsewhere. It is as an index of general or visceral arteriosclerosis that the radial artery has received particular attention. Hallenberger, noting the paucity of accurate investigations of arteries possibly involved in arteriosclerosis such as the radial, undertook such a study at Aschoff's request. He examined histologically the radial artery in about 80 cadavers, ranging in age from 8 months to 75 years and attempted to discriminate between physiologic and pathologic alterations in the vessel. Thayer and Fabyan's work is a clinico-pathologic study of the radials in 61 cases, comparing palpability and thickening with histologic findings and concluding that the unduly palpable radial artery is a danger signal of very possible visceral sclerosis. Hesse's

exhaustive monograph includes the removal in one piece of the subclavian, axillary, brachial and radial arteries and a gross and microscopic study of all these vessels, which permitted contrastive observations on normal and arteriosclerotic changes in vessels of both the elastic and muscular types of the upper extremities. In this way, she examined 41 cases at ages ranging from 2 days to 79 years and in addition a 6½ months' fetus. Though the amount of her material was small, she concluded that palpability of the arteries was independent of any morphologic change and due to tension and tonus of the vessel wall. Fischer and Schlayer⁴ many years previously had advanced a similar opinion based on a comparative test of the palpability and of the anatomic findings carried out on 75 arteries. They examined in each case the radial, brachial, femoral and carotid. In 50% of the cases where an intimal sclerosis was present, no thickening of the arterial wall could be demonstrated. In 75% of the cases where a very marked thickening or palpability of the artery was found, there was no anatomic sclerosis of the intima. The majority opinion seems to favor the view that the clinical condition of the radial artery offers no accurate information as to arterial conditions elsewhere. We, therefore, did not approach the problem from this angle.

In a series of 86 cases, ranging in age from birth to 84 years, we examined in each instance the radial and coronary arteries, in 25 cases the renal and splenic arteries as well, and in 7 cases a cerebral vessel also. We further studied 35 additional coronaries without accompanying radials. In each of the 86 cases, sections were taken from the anterior descending branch of the left coronary, the left circumflex and the right coronary arteries and the radial artery at the wrist. These were stained with hematoxylin and eosin and with Weigert's elastic stain and van Gieson. The same procedure was followed when other arteries were sectioned. While there was a certain amount of gross inspection in selecting the most likely part for section, the study was essentially microscopic and involved the examination of about 1700 sections.

The age distribution of the 86 cases as to decades was as follows: First, 6; second, 9; third, 9; fourth, 6; fifth, 23; sixth, 10; seventh, 17; and eighth and above, 6. The additional 35 coronary cases were likewise distributed through various decades. There was a partial selection of cases utilized in that we endeavored to get an average of individuals and ages that would represent what might be termed the normal age evolution of the vessels especially in the later years; and, again, another selection of cases suffering from diseases promising a maximum result in the way of vascular change. There were 73 males and 48 females in the series but we did not attempt an analysis on a sex basis.

Our scheme of procedure was first the systemic examination of the 121 available coronary arteries distributed widely through the

various decades. Thanks to the definite, clean-cut and extraordinary changes which take place normally and pathologically in these vessels and the detailed expositions of them by Wolkoff,⁵ Ehrich, de la Chapelle and Cohn,⁶ and Gross and his colleagues,⁷ the order and degree of their physiologic and pathologic change is almost standardized and to a lesser extent for muscular arteries generally.

The large coronary arteries show, both as to incidence and degree, among the greatest changes of any arteries in the body; this is especially the case with reference to muscular arteries, of which the coronary is an example. And among the elastic arteries, the aorta only approaches them in extent and frequency of alteration. Beginning with birth, plainly demonstrable changes are seen in even the first few weeks and continue until death, so that at 60 or 70 these vessels present a histologic picture that only remotely resemble the artery of the first decade. For details of this life-long evolution, one should consult Gross' article. Both physiologic and pathologic changes are predominantly intimal. At birth or in the first week, there may be slight thickening and beginning splitting of the internal elastic layer of the intima. This increases and longitudinal smooth muscle fibers appear between the split elastica. This constitutes the musculoelastic layer. The innermost elastic layer, the "secondary intimal elastic membrane," splits further to form the elastic-hyperplastic layer. The inner portions of the elastic-hyperplastic layer develop a preponderance of connective tissue and form the connective tissue layers. All of these layers, the musculoelastic, the elastic-hyperplastic and the innermost connective tissue layer progressively increase in thickness, mingle more or less, and collectively form an outstanding thick intimal layer soon equal to and often much thicker than the media. While these changes are taking place, straightening out of the usual undulations and breaks are seen in the internal elastic layer, and longitudinal muscle fibers from the media push over the intimal border causing "border disappearance" and constituting an "intermediary layer." Usually, however, it is quite easy to distinguish between the intimal and medial coats. The fine elastic fibers of the media first increase with years and then decrease and collagen fibers ultimately appear. But the media as well as the adventitia offer insignificant changes compared with the intima. All these coronary changes develop to reach a maximum about the end of the fourth or fifth decade and thus far the mural evolution is usually regarded as physiologic. Whether physiologic or pathologic, such intimal alterations are rather characteristic of muscular arteries as a whole. In other words, thus far, the coronary arteries act, as they look, like muscular arteries. After the fourth decade and especially in the sixth, atherosclerosis appears and caps the previous marked thickening with an eccentric addition which tends

considerably to narrow the lumen of the vessel. The media now suffers pressure atrophy and thins considerably. Both Wolkoff and Beneke⁸ emphasize the localization of these eccentric thickenings on the side of the artery that is turned toward the heart, the part that rests against the heart muscle. Another favored site is at the origin of branches. In fact, arterial thickening of any type seems to be especially prone to appear where branches leave the larger vessel. Following atherosclerosis, necrosis and calcification are common. It will be noted that this calcification, like the atherosclerosis, is intimal and scarcely ever is it found in the media. Here, therefore, the coronary acts like an elastic artery in which calcification, if it occurs, is regularly intimal. Ophüls⁹ thinks that from Wolkoff's description of the large branches of the coronaries, they resemble partly the elastic and partly the muscular arteries. The atherosclerotic changes are usually regarded as pathologic, with Wolkoff dissenting. Whatever the viewpoint, it is evident that such extreme alteration and thickening of the wall may lead to practical lumen extinction, either directly or finally through thrombosis.

Our sections of coronary vessels showed these changes quite clearly. Coronary vessels from 2 stillborns showed a perfect single-layered internal elastic layer. At 3 and 7 days, there was a little thickening. An artery of a 10-day-old infant exhibited definite elastic splitting and at 5 weeks a case showed a distinct musculo-elastic layer. At 2 months, the anterior descending branch of 1 case showed almost no change, while the right coronary showed splitting and an elastic muscular layer. At 1 and 3 years, these alterations were pronounced but still relatively slight. As the age increases, the intimal layer progressively and for the most part steadily thickens with one or more of the three layers described more or less prominent. Thus up to 40 or 50 years of age what one sees with not too analytic an eye is a gradual thickening of the intima as a whole. This gradually growing intimal collar seemed to us to be fairly uniform for the entire circumference of the vessel, though occasional thickenings were seen, notably at the branching of a vessel. There certainly was not the marked eccentric disposition seen in atherosclerotic formations. The degree of intimal thickening may be rather satisfactorily gauged by noting roughly its relation to the thickness of the media. Thus, the ratio of intima to media in thickness at birth and shortly after may be 1 to 6 or 8, after the first year and up to the tenth the ratio may be 1 to 2 or 3 and occasionally 1 to 1. In the second decade the ratios of intima to media do not vary much from the last of the first decade. But in the third decade, they are commonly 1 to 1 and not infrequently 2 to 1 or 3 to 1. The same ratios hold for the fourth decade. But again in the fifth decade, especially the latter half, the intima is found to be 2 to 3 times the thickness of the media and occasionally

higher with ratios 4 or 7 to 1 (atherosclerosis). In the sixth decade, ratios of 5 or 10 to 1 are common, due to the frequent appearance of atherosclerotic thickenings. Where atherosclerosis is absent, the ratio does not vary much from that seen in the fourth decade. The alternation of ratio is dependent almost entirely upon intimal change rather than medial. The coronary arteries, then, from birth to death gradually thicken, almost exclusively through intimal change. Up to 40 years this is roughly uniform and may be considered hyperplastic and physiologic. After 40 there is not much change of this type, but commonly supplementary eccentric addition to the intimal thickness by atherosclerotic formation. This may be totally expressed in the altering ratio of intimal to medial thickness and this may be considered an index of coronary sclerosis, physiologic or pathologic.

Radial artery changes have been analyzed generally along the same lines, Hallenberger, Thayer and Fabyan and particularly Hesse describe primary splitting of the elastica with the development of the elastic muscular layer, then the elastic-hyperplastic layer and finally the connective tissue zone or thickening. Upon this may or may not be superposed atherosclerosis: all agree that in the radial this is uncommon if not actually rare. The radial is a much smaller artery than the main coronaries and the changes in it are infinitely less than in the coronary and proportionately difficult to analyze meticulously.

Surveying our sections of 86 radials in advancing decades, we observed in the radial of the stillborn the perfect single-layered internal elastic layer immediately beneath the lining endothelium as in the coronary. At 1 and 3 years of age, splitting of the internal elastic layer was seen, but little else except a very slight thickening where branches leave. Toward the end of the first decade, there may be noted a very slight thickening in addition to splitting, the beginning of the musculoelastic layer. Radials at 12, 13, 14, 16 and 17 years showed only a slight exaggeration of this, changes that ordinarily would be passed over. One radial at 16 years exhibited almost no alteration. In radials at 12, 13 and 14 years, the media appeared thickened but we thought this might be due to the postmortem contraction of the arterial wall that Hesse found so marked in the young. From 21 to 30 years, this thickening of the intima, due to splitting and proliferation of the elastic layer, together with the appearance of muscular and connective tissue fibers, progressed steadily but only to a very slight degree. Again in the fourth decade, from 31 to 40, the increase continued but not greatly. In this decade one could see in the Weigert sections definite multiple elastic layers and in the hematoxylin and eosin sections an increased breadth of intima dotted with cross-sections of nuclei and fibers. There was a decided increase of thickening in the fifth decade, from 40 to 50 years, in which we were able to

examine 17 radicals. There now was seen a distinct though slight intimal collar made up mostly of split elastica and connective tissue. Longitudinal sections showed connective tissue arranged lengthways between the elastic layers. There is supposed to be a certain amount of longitudinally arranged unstriped muscle with this connective tissue, but it is difficult to distinguish even with the van Gieson stain. From 50 to 60 and from 60 to 70 there was still a fairly steady though not excessive increase in the thickness of the intimal wall. Most of the radical change is intimal and this intimal change occurs particularly between 45 and 65. After 65 there is not much intimal thickening, but as the media shows some degeneration and slight thinning particularly after 60, casual observation may give the impression of rather marked intima increase. We measured the medial of all radials and found the thickness of the middle coat increased up to the middle of the third decade, after which it remained practically stationary until the middle of the seventh decade, when the media showed a slight thinning. All this change is of the type seen in the coronary and usually regarded as physiologic, though in the radial the discrimination between musculoelastic, elastic-hyperplastic and connective tissue layers is much more difficult, if not at times impossible, on account of the greatly less degree of alteration. Atherosclerosis as it occurs in the coronary is, for practical purposes, not seen in the radial. On this paucity of lipoid deposit or atherosclerotic formation all writers agree, and Nordmeyer¹⁰ found no fat in the radial artery. Her sections, like ours, were taken at the wrist. She refers to the fact that Hesse in higher sections of the radial found more sclerosis. In our series of 86 radials, we found only in 3 evidences of slight lipoid deposits in the thickened intima and in no case any atherosclerotic plaques. Certainly the striking extreme eccentric atheromatous thickening so characteristic of the coronary is not seen in the radial. The maximum change in the radial artery, consisting of a roughly uniform intimal collar of elastic and fibrous connective tissue and achieved between 45 and 65 years is comparable in kind but not in degree with the probably physiologic variety seen in the coronary before 40 years. We should say that the thickest radial seen at, say 65 years, and above, compared in kind and degree with that of the coronary change at about 20 years of age.

These differences in radial and coronary vessels are strikingly brought out in a comparison of the ratios between the intima and media in the two vessels, as the changes in both arteries are dominantly intimal. In comparison with the intimal-medial ratio in the coronaries, previously described, in the radial, the intimal-media ratio of 1 to 8 or more found in the first decade shifts much more slowly, until between 30 and 40 years of age it may be 1 to 4 or 5. After the fourth decade, the intima thickens more and

the ratio is then 1 to 3 or 4 and later 1 to 2 or 3. Only occasionally is the ratio 1 to 1, the intima equalling the media in thickness, and it exceeds the media only rarely and locally in one of the cushion-like thickenings. The difference in ratio is not due to thickening of the media, which changes but little in diameter in the radial after 30. This notable difference between radial and coronaries we have attempted to make clear in a series of comparative drawings of the radial and coronary walls drawn to scale as far as the intimal and medial ratios are concerned (Figs. 1, 2, 3 and 4). The compared radial and coronary arteries at any given age are always from the same case. The coronary is, of course, much larger than the radial and this is not seen in the drawings but the actual breadth relation between the intima and media of each vessel has been strictly maintained. The variation in intimal thickness at different ages and in the single sections is outlined in the black silhouette while the media is shown in white. They represent the progressive mural thickenings from birth to old age. We did not attempt to select or avoid cases with diseases supposedly predisposing to arteriosclerotic change, as both arteries are presumably liable. But the majority died with disease having no known definite relation to arterial change, and we think these drawings represent what may be expected in the way of change at different ages in the respective vessels. It is interesting that the coronary in the patient, aged 32, dying of acute leukemia, showed almost as much change as the coronary of the 84-year-old patient dying of nephrosclerosis and that while the radial is relatively thickened in both these cases, they were scarcely so in other cases with marked coronary thickening. It is plain from these drawings the coronaries increase early, progressively and greatly, while the radials show a relatively slight and insignificant change.

We have so far purposely omitted mention of medial calcification (Mönckeberg's sclerosis), as it apparently has no bearing on or relation to the intimal changes just discussed. Mönckeberg's sclerosis, as is well known, is a disease of muscular arteries, particularly of the peripheral vessels and is much more common in the lower extremities. Lange,¹¹ in 300 cases, found medial calcification in the lower femoral in 97%; posterior tibial, 87%; anterior tibial, 83%; brachial, 2%, radial, 18%; and ulnar artery, 14%. It is a pretty good rule that atherosclerosis increases centripetally and medial calcification centrifugally. Atherosclerosis attacks the elastic arteries; medial calcification, the muscular arteries. In 9 of our 86 radials there was well-marked medial calcification. This was distinctly medial and in none of our cases was there intimal calcification. Some writers, Thayer and Fabian, for example, think intimal calcification of the radial not uncommon, but this is not our experience. Both Hallenberger and Hesse found calcification along the internal elastic layer. Some of our sections showed this appearance, but it

Radial

Age

Coronary

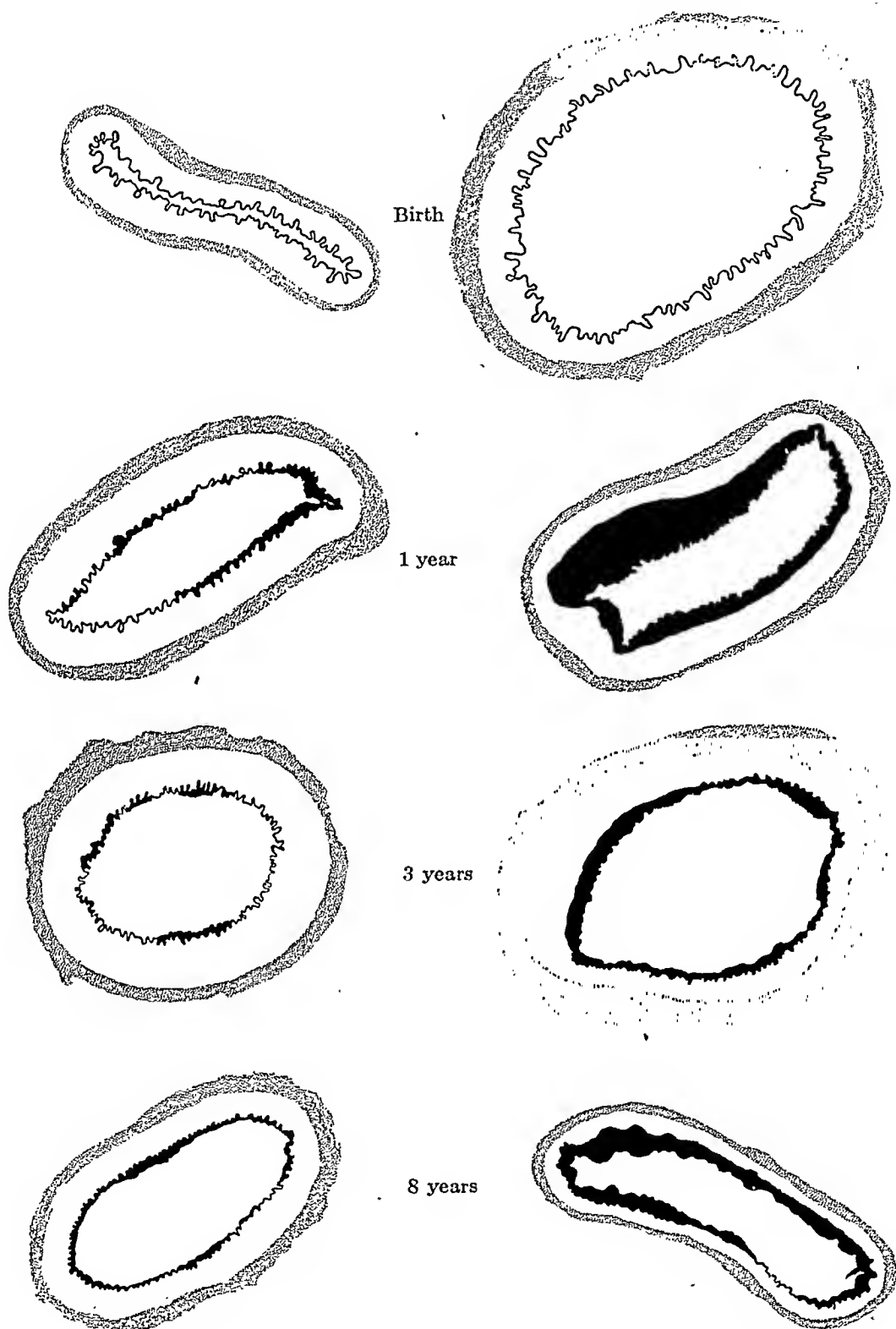


FIG. 1

FIGS. 1, 2, 3 and 4.—(34 small drawings.)* Cross-sections of the radial and coronary arteries, each from the same case, at various age periods as follows: birth, 1, 3, 8, 14, 17, 21, 28, 32, 37, 42, 49, 53, 60, 64, 70, 84 years. Intima in black, media in white, adventitia stippled, drawn to scale to show relation of intima to media in thickness.

* The accurate drawings were done by F. T. Kepler.

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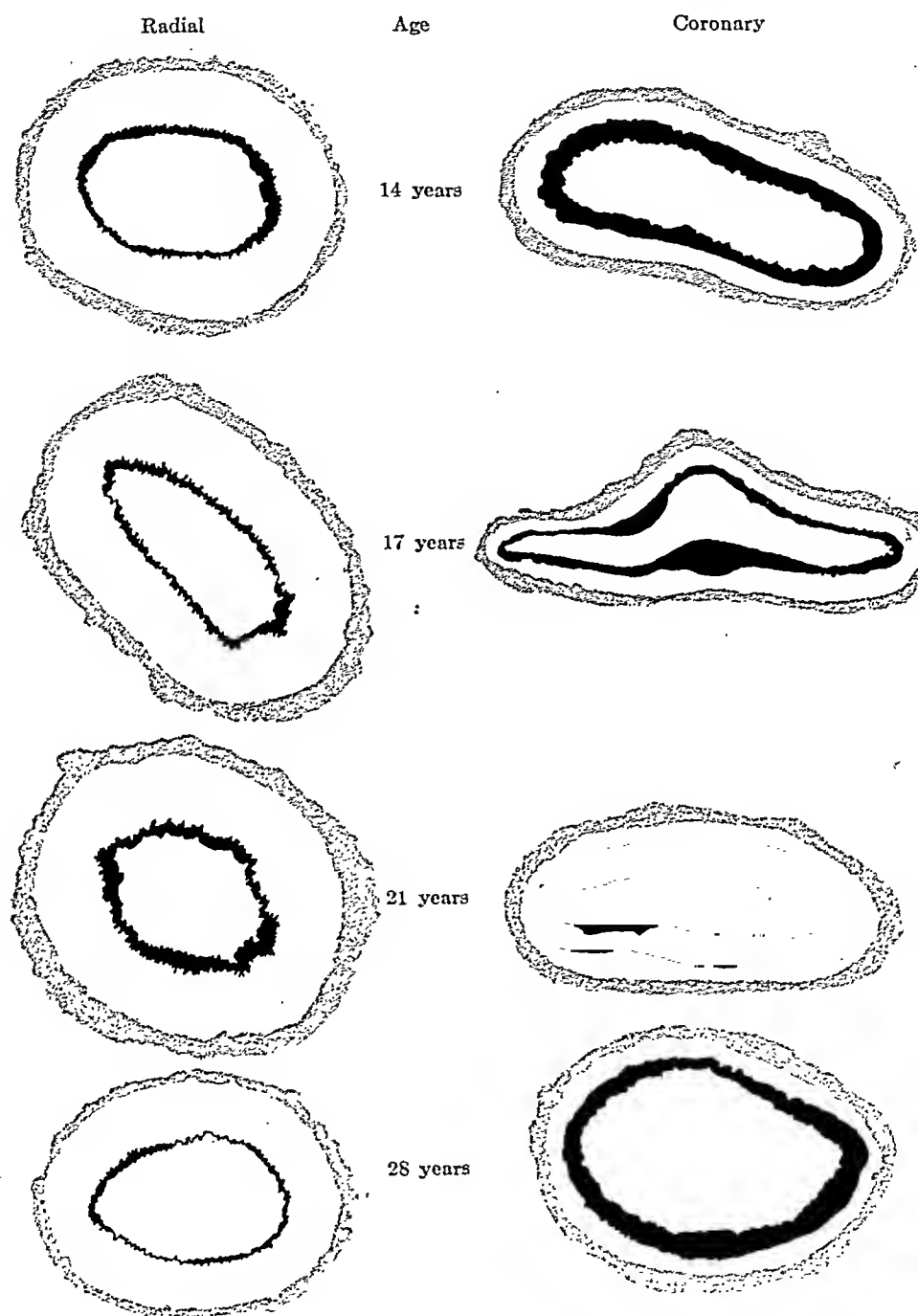


FIG. 2

Radial

Age

Coronary

32 years

37 years

42 years

49 years

53 years

FIG 3

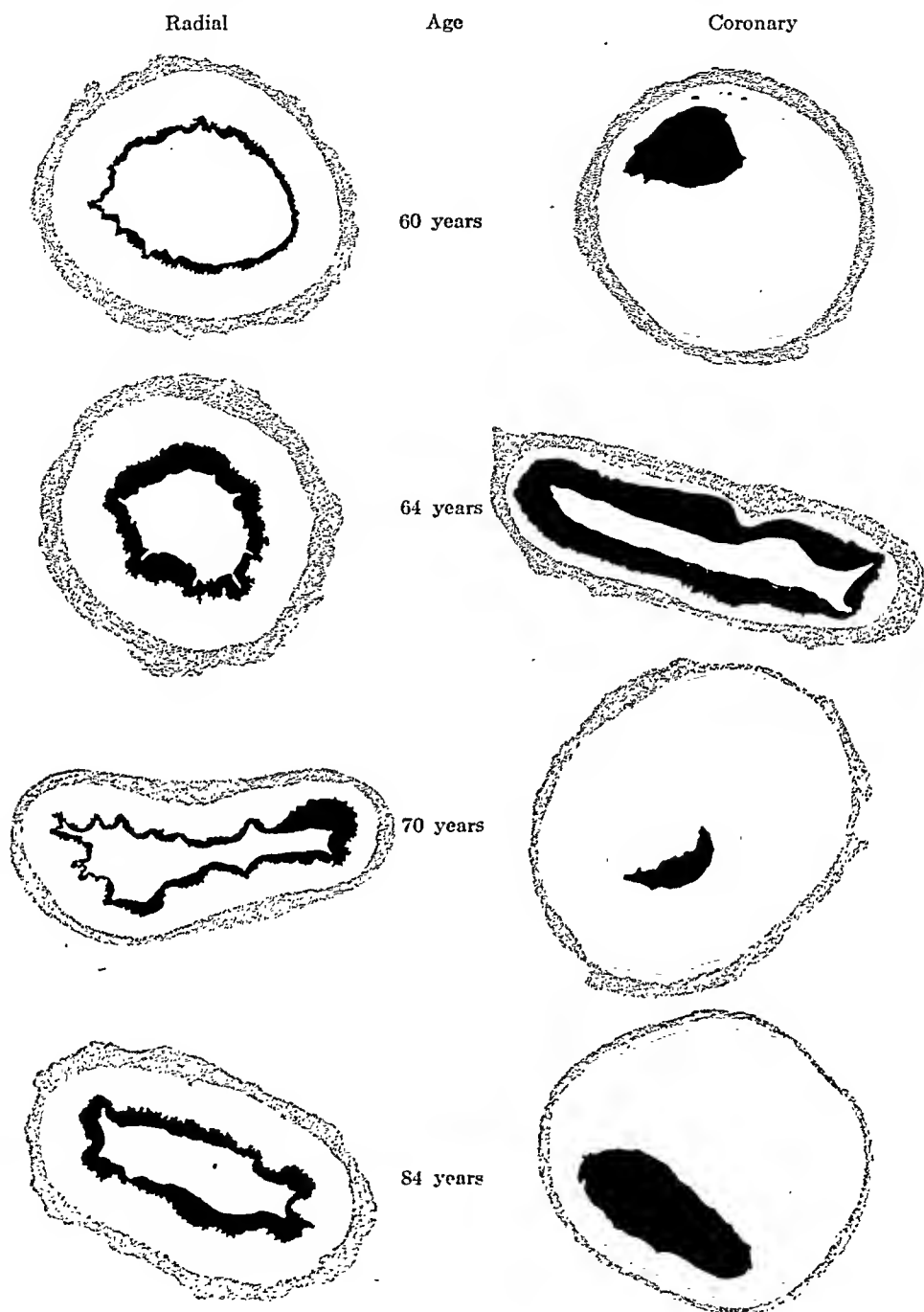


FIG. 4

seemed to us that in these cases the calcification was really medial or at least primarily so and extending into the intima and then hardly across the border. In fact, it seemed to us noteworthy that radial calcification was almost invariably medial. On the other hand, we scarcely ever saw medial calcification of the coronary. Rarely there was a very slight degree of it, but not at all of the Mönckeberg type, while intimal calcification was, of course, extremely common in the atherosclerotic regions in the coronaries. This localizing tendency in Mönckeberg's sclerosis was well illus-

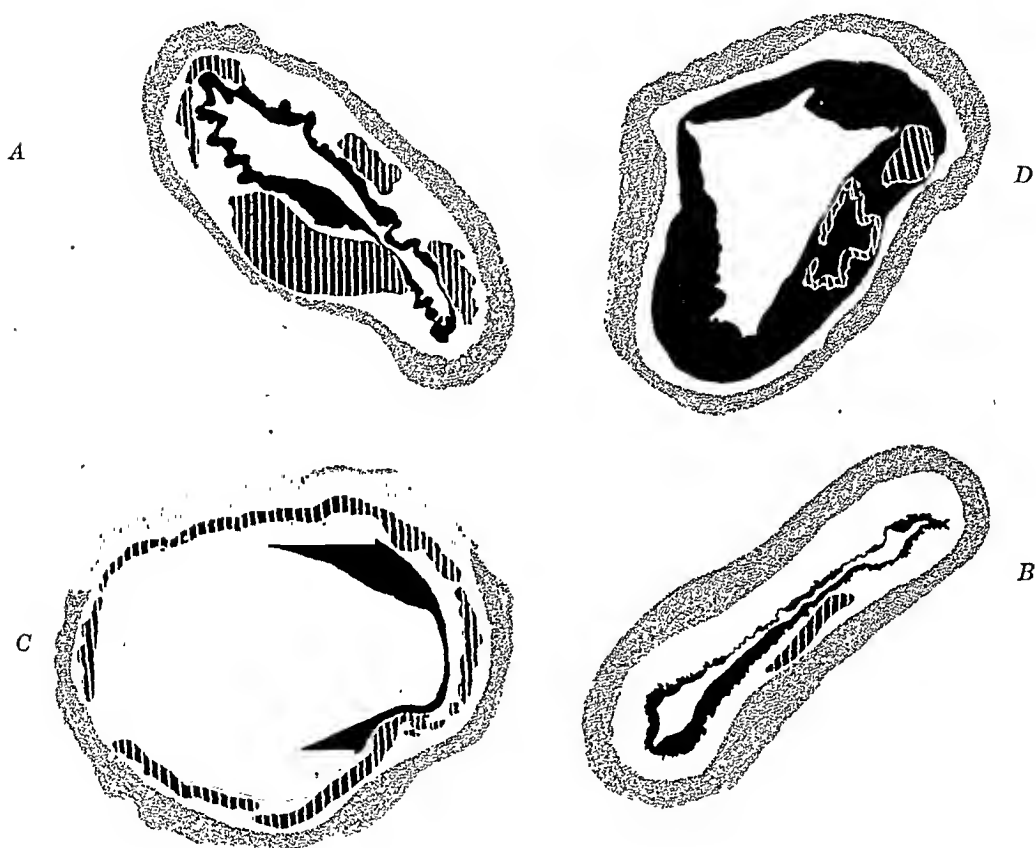


FIG. 5.—Radial, A; renal, B; splenic, C; and anterior descending branch of left coronary artery, D; and localization of calcified areas. Intima black, media white, adventitia stippled and calcified areas barred. Case 21. Patient aged 68 years.

trated in 1 case which showed extreme medial calcification in the radial and similar change though of less degree in the renal, splenic and vertebral arteries, while the coronary from the same case presented an extreme degree of intimal calcification but no involvement of the media (Fig. 5). Similar findings were obtained in another case which showed radial, renal and splenic medial calcification and coronary intimal calcification. It is curious that the coronary, structurally a muscular artery, acts, as far as atherosclerosis and calcification are concerned, like an artery of the elastic type.

There were 25 cases in which the radial artery was compared with the main renal and splenic arteries from the same patient and 7 cases in which a cerebral artery was examined as well. Of these, 80% were from subjects of 45 to 78 years. The renal, a muscular artery, is larger than the radial just as the splenic, also a muscular artery, is larger than the renal. In many instances, one artery would show decided change and the others little; or two might show change and a third but little. The changes were mostly intimal in all, but of unpredictable degrees. On the whole, we found renal changes less than radial and splenic changes more than radial. The ratio of intima to media in the renal vessel after 50 was often 1 to 5 up to 1 to 8, while the radials for the same period showed a ratio of 1 to 2 up to 1 to 5. The splenic artery noted for its tortuosity was expected to show great changes but single sections, though taken from supposed favorable sites, showed not infrequently surprisingly little change, often not more than the radial and at times less. The splenic ratio was about like the renal. The splenic, however, and occasionally the renal showed marked eccentric atherosclerotic plaques sometimes with calcification. These thickened the wall decidedly and altered the ratio locally to 5 or 10 to 1. Such a finding is almost unknown in the radial. There were 2 such plaques in 25 renal arteries and 5 in 25 splenic arteries. On the other hand, we found a renal artery from a man of 77 like that of a child of 10 with an almost perfect internal elastica. The media of the renal and splenic arteries showed, compared with the radial, an apparent diminution of muscle fibers in later life with the appearance of hyalin or bluish areas suggestive of mucin. This is seen to some extent, but much less, in the radial of older people. In examining the cerebral vessels, the normal thickness of the internal elastica and the thinness of the muscular layer was kept in mind. We examined 9 vessels in 7 cases, 2 vertebrals, 5 basilar, 1 middle cerebral and 1 internal carotid. The changes were a little more marked than in the radial. They are predominantly intimal. The media is so thin that the ratio is not so significant as in the radial or coronary. The intimal-medial ratio of thickness varied early and in milder changes from 1 to 2 to 1 to 4 but shifted to 2 to 1 to 4 to 1. Atherosclerotic intimal plaques are apparently common here and we found 2 in the 7 cases with marked eccentric thickening. In another case (Fig. 6) in which there was basilar thrombosis there was a very thick calcified plaque and a similar one in the vertebral artery while the radial showed only moderate change of the physiologic type. The intimal-medial ratio of the basilar in this was 10 to 1 as against a 1 to 4 in the radial. The coronary changes of the same case were marked and atherosclerotic but not extreme.

The distribution of calcification in this group of 25 cases was of some interest. As has been already noted, when the radial calci-

fication was medial (the Mönckeberg type), calcification, if found elsewhere as in the renal, splenic or cerebral vessels, showed the same localization while coronary calcification; if present, was almost invariably intimal. Of course, calcification either medial or intimal was not necessarily found in the other vessels when present in the radial or *vice versa*. This might be due in part to the fact we did not make multiple sections of each vessel. Whether or not there was found Mönckeberg sclerosis, the presence of an atherosclerotic sclerotic plaque presented an invitation for lime deposits and such

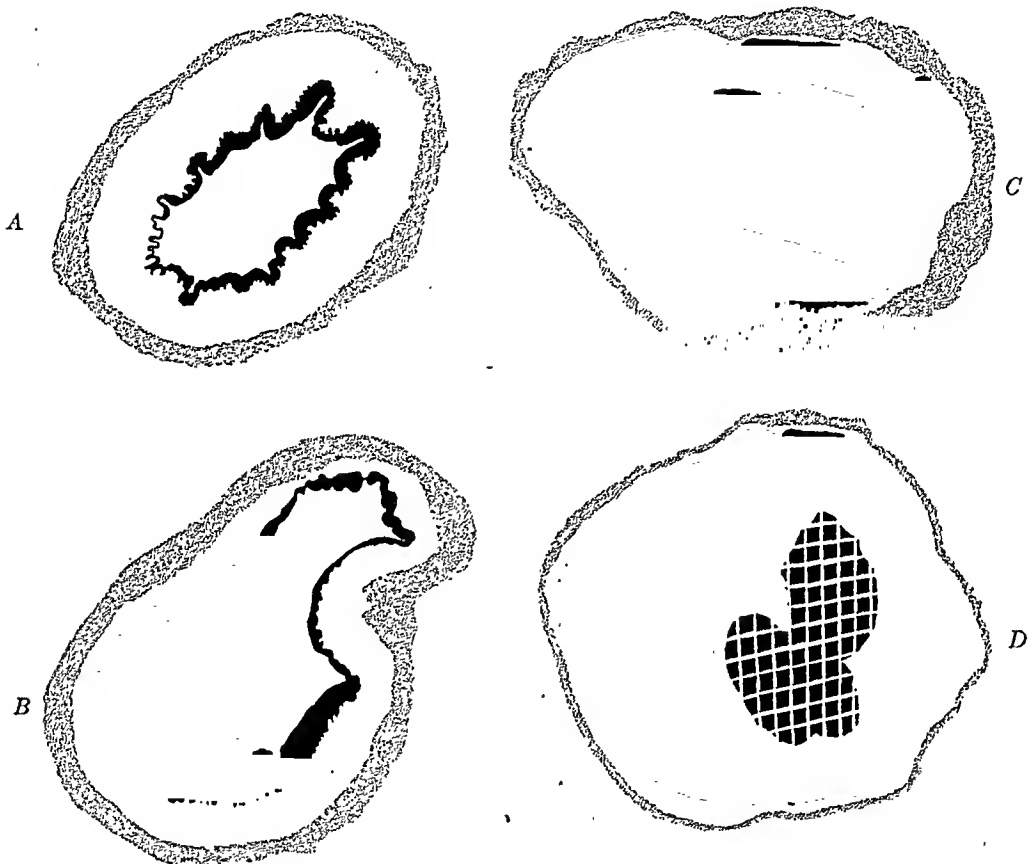


FIG. 6.—Showing variations in intimal thickening and sclerosis in radial, A; anterior descending branch of left coronary, B; left vertebral, C; and basilar arteries, D. Intima black, media white, adventitia stippled, thrombus in basilar cross-hatched. Case 19. Patient aged 60 years.

an intimal change seemed entirely independent of the medial condition. In these 25 cases we found 4 examples of radial calcification (all medial); 3 renal (1 intimal and 2 medial), 7 splenic (3 intimal and 4 medial), 2 cerebral (both medial), and 12 coronary (all intimal). These figures are somewhat of a commentary on the type of arteriosclerosis found in such vessels.

Though our material was rather meager, the vessels were scrutinized with respect to the relation of certain infections or other con-

ditions to arteriosclerotic changes. McCallum¹² finds little evidence that infections play a great part in the pathogenesis of arteriosclerosis but notes that there seems to be a definite association of arteriosclerosis with such diseases as diabetes, arteriosclerotic nephritis and cholelithiasis. Four of our cases of rheumatic infection showed no more radial or coronary change than found in many other conditions. Two of 4 cases were examples of rheumatic pancarditis in boys of 10 and 11. The boy of 11 had a heart weighing 450 gm. but even with this marked hypertrophy there was less coronary change than usual. The other 2 cases were adults with marked degrees of rheumatic mitral and aortic disease but radial and vascular coronary changes were in no way exceptional.

There were 4 cases of diabetes, aged, respectively, 37, 47, 60 and 60. The 37-year-old case showed no more than average change for that age. The other 3 showed little radial change but very marked coronary sclerosis and 1 died of coronary disease. This last case showed thrombosis of the right coronary but all his coronary vessels showed extreme atherosclerosis. The patient, aged 47, was one of diabetes terminating with erysipelas. This case showed extreme atherosclerotic narrowing of the anterior descending branch of the left coronary artery with reduction of the lumen almost to complete closure; yet the patient gave no signs and was not suspected of coronary disease. Two of the diabetic cases, in which the renal and splenic arteries were also examined, showed in 1 case atherosclerosis of the renal and in the other atherosclerosis of the splenic with calcification of the intimal plaque.

There were 8 cases of hypertension with marked nephrosclerosis. The radial changes in these were relatively slight, certainly not a feature. On the other hand, the coronary changes were extreme in 5 out of 8. These findings were more significant in 4 of the cases in which the ages were respectively 16, 22, 24 and 25 and, therefore, at a period in which the age factor or general atherosclerotic development could not be invoked to explain the sclerosis. In patients of 16 and 22, the ratio of intima to media was as high as 10 to 1 and the patient at 24 shows in the illustration (Fig. 7) the striking contrast between radial and the various coronaries. In 8 cases of hypertension with only slight or moderate renal findings, the radial changes were slight to moderate, the latter usually in late age period while the coronaries in 4 out of 8 exhibited extreme sclerosis, though the age factor here had to be considered. There were 6 cases with the clinical diagnosis of coronary thrombosis. Five of these showed extreme coronary atherosclerosis and thrombosis; but 1, aged 46, showed coronary thrombosis with very little arteriosclerosis of the coronary, though there was Mönckeberg's sclerosis of the radial. In the other 5 cases the radial showed no significant change except one which showed medial calcification.

There were a number of cases, at least 11, in which there was ex-

treme coronary disease without the clinical diagnosis or suspicion of coronary involvement. A number of these were examples of hypertension with or without nephrosclerosis and 6 died of cerebral hemorrhage. Two cases showed this extreme coronary arteriosclerosis with

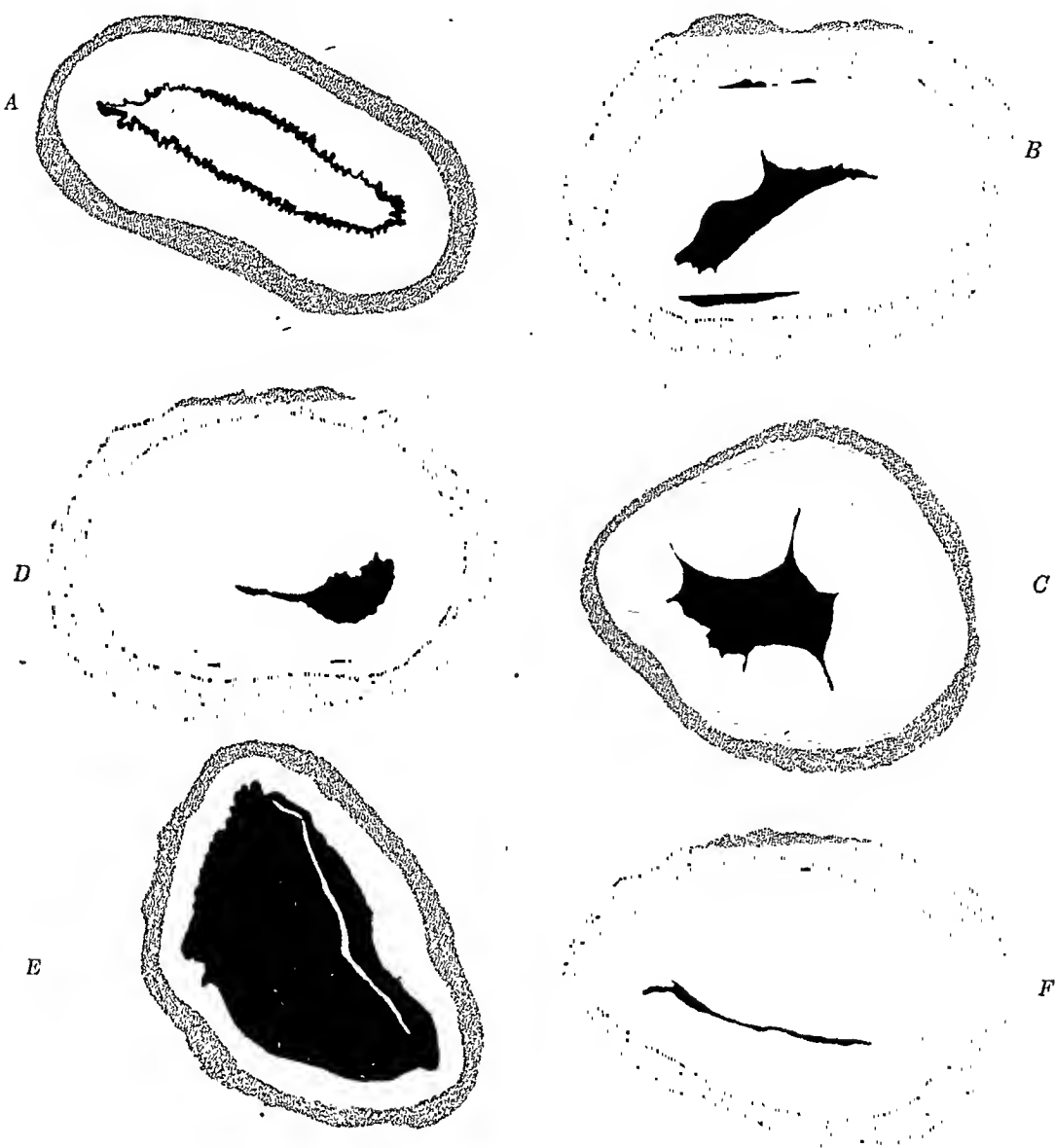


FIG. 7.—Showing variations in intimal thickening and sclerosis in radial, *A*; right circumflex, *B*; left circumflex, *C*; anterior descending branch left coronary, *D*; branch of anterior descending artery, *E*; posterior descending branch of right coronary, *F*. Intima black, media white, adventitia stippled. Case 82, patient aged 24 years.

almost complete closure of the vessels but had no kidney or heart disease or hypertension. One, aged 32, already noted, died of acute leukemia; another, aged 53, died of cancer of the rectum. These 2 patients had only the very slightest radial alteration. Two cases

of toxic goiter, one 44 and one 46, showed moderate changes in the radial with an intimal-media ratio of 1 to 3, while the coronary vessels were only slightly altered and decidedly under the average for the age. Syphilis though present in a number of cases was so involved with other diseases and conditions that it could not satisfactorily be correlated with vascular change in the radials or coronaries.

Summary. There is here presented a study of age period and arteriosclerotic changes in the radial artery in which a comparison was made between the coronary and radial vessels in the same patient in a series of 86 cases. As the changes in both are predominantly intimal, a rough but satisfactory index of change was found in the ratio of intimal to medial thickness in the two vessels. The coronary intimal-medial ratio rose rapidly from 1 to 6 or 8 to 1 to 3, 1 to 2 and 1 to 1 until in the third and fourth decades the intima equaled and not infrequently exceeded the media in thickness. After 45 years, and especially in the sixties, the addition of atherosclerotic changes raised the intimal-medial ratio still further to readings from 6 to 1 to 10 to 1. On the other hand, the radial intimal-medial ratio rose slowly to reach a maximum between 45 and 65 years, a maximum, however, which is minimal compared to coronary alterations and in which the intimal-medial ratios seldom ever go above 1 to 1 and are usually 1 to 3 or 4. This is due to the slight degree of so-called intimal physiologic thickening, compared to the great degree that obtains in the coronaries, plus the fact that augmentation of intimal thickening by atherosclerotic plaques is practically missing in the radial while it is routinely found in the coronaries after 50 years. Thus the thickest radial, found say at 65 years, has no more change than that seen physiologically in the coronary vessels at about 20 years. This inequality of age transitions is well illustrated in Figs. 1, 2, 3 and 4.

A further comparison of radials with splenic and renal arteries in 25 cases and cerebral vessels in 7 cases showed that in many instances the physiologic intimal thickening was only a little more marked than in the radial, but that these other vessels were subject at times to marked atherosclerotic developments notably absent in the radial.

Mönckeberg's medial sclerosis was present in 10% of our radials but was not found in any of the coronaries, though intimal calcification of these vessels was very common. Medial calcification, however, was found in corresponding splenic, renal and cerebral vessels along with intimal calcification of the coronaries. The Mönckeberg type of sclerosis seemed entirely independent of and unrelated to the presence or absence of atherosclerosis, except that they are both commonly found after 50 years.

Scrutinized as to the relation of certain diseases to arteriosclerotic change, it was found in the small series available that cases of diabetes and malignant and benign hypertension showed marked or extreme coronary sclerosis, while the corresponding radial was little affected. Six cases of clinical coronary disease with typical lesions showed little radial change, except one which presented Mönckeberg's sclerosis. Advanced coronary sclerosis was also unexpectedly encountered in a number of cases in which the preceding history and disease seemed entirely unrelated to such vascular change. Such cases were not suspected during life of coronary disease; certainly the radial artery gave no information.

Conclusions. The present study suggests: 1. That both age period changes and arteriosclerotic changes are maximal in the coronary arteries and minimal in the radial arteries and more or less intermediate in other vessels, such as the cerebral, splenic and renal arteries.

2. That atherosclerosis in the radial is such a rarity as to be negligible.

3. That the anatomic condition of the radial artery has no bearing on visceral sclerosis.

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THE RELATION OF CORONARY SCLEROSIS TO SYMPTOMS AND ITS DISTRIBUTION IN 242 FATAL CASES.*

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MUCH has been written on the subject of coronary disease, particularly in the last two decades, and some excellent reviews have been published recently. Yet comparatively little is available for a correlation of coronary arteriosclerosis and the clinical signs and symptoms. This paper is an attempt to correlate the pathological findings with the clinical picture in 242 fatal cases.

Material. Part of the material was obtained from those autopsy protocols of the University Hospital from 1926 to 1933 of which slides were accessible for study of the coronary arteries. Only those mentioning sclerotic coronaries, macroscopically or microscopically, were selected. Of 207 cases assembled, 15 were later rejected because of incompleteness, leaving 192 cases for study. Of the slides from the 192 cases, 99 showed one or more of the main subepicardial branches of the coronary arteries, while the remaining 93 showed only secondary subepicardial or intramyocardial branches. This constituted Series 1. To supplement this material a group of 50 current autopsies were more extensively studied: Series 2. Cases were selected only where sclerosis of the coronary arteries was present grossly and sections were taken of the six main superficial branches, 9 cases coming from the University Hospital and 41 from the Philadelphia General Hospital. Sections were made also of the kidney, liver, spleen, adrenal and pancreas, to compare arteriosclerosis in other organs with that in the coronaries. Sections were taken from the Anterior Descending Branch, 1 to 3 cm. from its origin in the aorta; Left Circumflex, just below the tip of the auricular appendage; Left Marginal Branch, varied but usually where the artery was thickest; Right Circumflex, 2 to 3 cm. from its origin in the aorta; Right Lateral Branch, as the artery curves down to take the lateral margin of the right ventricle; the Posterior Descending, 1 to 2 cm. from the auriculo-ventricular groove. After microscopic examination the sclerosis of the arterial wall was classified in the following code:

1. *Mild*: intima less than $\frac{1}{2}$ the thickness of the wall (Fig. 1).
2. *Moderate*: intima from $\frac{1}{2}$ to as thick as the rest of the wall (Fig. 2).
3. *Marked*: intima thicker than the rest of the wall (Fig. 3).
4. *Very Marked*: intima so thick that the lumen as found in the contracted, fixed material of the microscopic section was represented by a narrow tube or mere slit (Fig. 4). (It is recognized that during life the lumen was undoubtedly much larger.)
5. *Occlusion*: occlusion with or without canalization.

Analysis of Material. *Age.* In Series 1, there was 1 case in the first decade of life, 1 in the second, 10 in the third, 18 in the fourth, 33 in the fifth, 43 in the sixth, 55 in the seventh, 29 in the eighth, and 2 in the ninth. In Series 2, there were 2 in the fourth decade,

* This work was performed in partial fulfillment of the requirements for the Degree of Master of Science (Pathology) of the Graduate School of Arts and Sciences of the University of Pennsylvania.

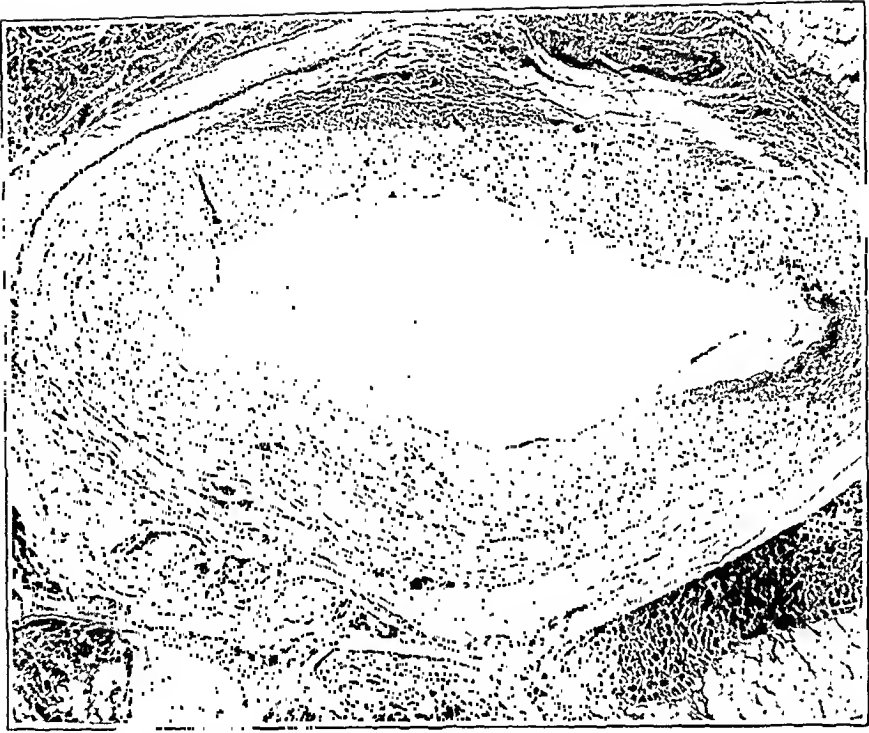


FIG. 1.—Photomicrograph of section of the anterior descending branch of the left coronary artery showing mild degree of sclerosis. The internal elastic membrane, limiting the media can be seen from 1 to 4 mm. from the lumen.

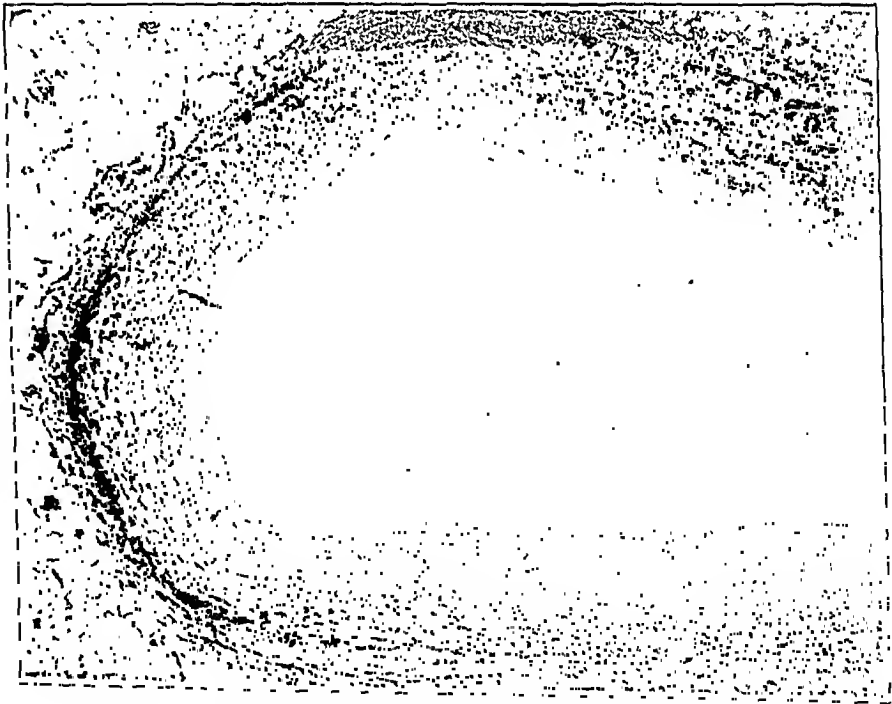


FIG. 2.—Moderate sclerosis. The internal elastic membrane lies from 7 to 10 mm. from the lumen.

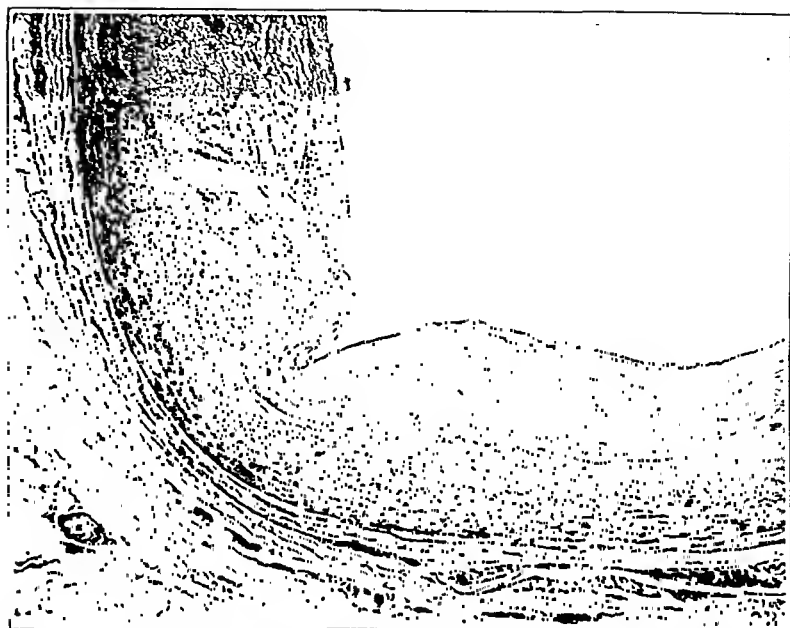


FIG. 3.—Marked sclerosis. The internal elastic membrane lies less than 1 cm. from the outer margin of the media.



FIG. 4.—Very marked sclerosis

6 in the fifth, 15 in the sixth, 12 in the seventh, and 15 in the eighth decade. This made the combined series have 1 case in the first decade of life, 1 in the second, 10 in the third, 20 in the fourth, 39 in the fifth, 58 in the sixth, 67 in the seventh, and 44 in the eighth, and 2 in the ninth decade.

Sex. In Series 1 there were 124 males (64.6%) and 68 females; in Series 2, 32 males (64%) and 18 females. In the two series, the per cent of males to females is almost identical, the combined ratio being 156 males (64.5%) to 86 females (35.5%).

The degree of sclerosis in the 99 cases having a large branch of the coronary artery is shown in Table 1.

TABLE 1.—DEGREE OF SCLEROSIS IN THE 99 CASES EXHIBITING LARGE BRANCHES.

Degree of sclerosis	1	2	3	4	5
	Mild	Moderate	Marked	Very marked	Occlusion
Number of cases	18	20	29	26	6

Thus, of the 99 cases, 61 (61.6%), had marked sclerosis; 38 had mild to moderate; and, as will be mentioned later, 91.66% of the cases with cardiac pain were in the marked sclerotic group.

Of the 50 cases studied in greater detail, the degree of sclerosis of the six main branches of the coronary arteries and veins is tabulated in Table 2.

TABLE 2.—SCLEROSIS IN SIX MAIN BRANCHES OF CORONARY ARTERIES AND VEINS.

	Anterior descending.		Posterior descending.		Left circumflex.		Right circumflex.		Left lateral.		Right lateral.	
	Artery.	Vein.	Artery.	Vein.	Artery.	Vein.	Artery.	Vein.	Artery.	Vein.	Artery.	Vein.
Mild . . .	2	17	20	11	4	11	4	6	18	3	19	2
Moderate . .	4	2	9	..	2	1	11	..	9	1	13	..
Marked . . .	23	..	12	1	38	1	25	..	12	..	12	..
Very marked .	18	44	5	17	5	44	7	35	5	17	2	14
Occluded . .	3	1	..	3
Not on slide .	..	7	1	8	..	19	4	8	2	8
Normal	16	3	34	..	29	..	25	2	38	2	40

This showed, as one would expect, that the arteries were more sclerotic than the veins. The anterior descending branch was "very markedly" involved in the sclerotic process more than twice as many times (18 times) as the next most frequently involved (7 times) which was the right circumflex. The left circumflex was more uniformly "markedly" involved (38 times); but it was only 5 times "very markedly" involved. In a "marked" to "occluded" grouping, the order of frequency ran: anterior descending and left circumflex (each, 44 times), right circumflex (35 times), posterior descending and left lateral (each, 17 times), right lateral (14 times). The veins accompanying the different branches were often found mildly sclerosed and a few times moderately. Those accompanying the anterior descending branch were more frequently involved

(19 times) than those accompanying the lateral branch of the right coronary (2 times).

Other organs were studied to determine the degree of arteriosclerosis present and the findings tabulated in Table 3.

TABLE 3.—SCLEROSIS OF MEDIUM AND SMALL ARTERIES OF OTHER ORGANS OF THE 50 CASES OF SERIES 2.

	Kidney.		Spleen.		Liver.		Lungs.		Adrenals.		Pancreas.	
	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.	Medium sized artery.	Arterioles.
Mild	5		6		20	10	24	19	14	3	18	5
Moderate	18	14	17		11	31	13	19	16	19	17	24
Marked	18	20	16	10	5	8	2	2	2	12	3	9
Very marked	24 6	14	20 4	38	5 2	1	3 1	9	3 1		5 1	1
Normal												
Not present	3	2	5	2	11	1	9	1	17	16	9	9

This table showed that the arteriosclerosis was pretty well generalized in the 50 cases of Series 2; but that it was present in varying degrees in different organs. The kidney and spleen showed marked arteriosclerosis comparable with the heart; it must be recalled that the material was selected on the basis of the existence of coronary sclerosis.

The kidney and spleen were more severely affected than the liver as far as very marked changes were concerned. In the groups of "moderate" sclerosis, the distribution in the different organs was surprisingly uniform. This agreed with Wartman's¹ observations that the kidney and spleen were most frequently and severely involved; but it differed as far as generalized arteriosclerosis was concerned. At least, it is justifiable to say that in most cases with arteriosclerosis of the coronary vessels, arteriosclerosis was also present in vessels of other organs to a varying degree and most marked in the kidney and spleen.

Cardiac Pain. Of special interest was the question as to whether a history of cardiac pain could be correlated with the presence and intensity of coronary sclerosis. With the realization that this method would include some cases of "non-coronary" pain, it was all the more surprising that only 15.91% of Series 1 (30 out of 192 cases) showed pain of cardiac origin; and 14% (7 out of 50 cases) in Series 2 (average for the two series was 14.95%) (Table 4). In Series 1, 19 were males (1 colored); in Series 2, 5 were males. Of the females, there were 11 in Series 1 and 2 in Series 2. This made a total of 24 males and 13 females, almost 2:1.

TABLE 4.—CARDIAC PAIN ACCORDING TO DECADES IN 242 CASES.

	20-29	30-39	40-49	50-59	60-69	70-79	Total.	%
Series 1	1	2	7	7	10	3	30	15.91
Series 2			1	3	3		7	14.00

Of the 30 cases in Series 1 having cardiac pain, for 17 there were slides with large branches of the coronary arterics. Table 5 shows the degree of sclerosis in the 17 cases, together with the 7 cases of Series 2.

TABLE 5.—DEGREE OF SCLEROSIS IN CASES WITH CARDIAC PAIN.

	Mild.	Moderate.	Marked.	Very marked.	Occlusion.
Series 1 . . .		2	4	8	3
Series 2 . . .			3		4
		—	—	—	—
Total . . .		2	7	8	7

As was to be expected, most of the cases with cardiac pain (22 out of 24, or 91.7%) showed severe sclerosis; while only 2 had moderate sclerosis. No case of mild sclerosis showed pain of cardiac origin. In Series 2, 4 out of 7 cases with cardiac pain (57%) were due to occlusion.

Analysis of Signs and Symptoms. Clinical analysis of the signs and symptoms was tabulated in Tables 6, 7 and 8. Only clinical symptoms referable to the heart were recorded; and cases in which dyspnea or pain in the chest was present with pneumonia or in which the liver was found enlarged in the presence of cancer of the stomach, and so forth, were discarded.

TABLE 6.—SIGNS AND SYMPTOMS OF CARDIAC DISEASE IN BOTH SERIES (242 CASES).

Number cases.	Palpitation.	Precordial discomfort.	Precordial pain.	Dyspnea.	Congestive failure.				
					Râles or impairment at bases of lungs.	Cyanosis.	Edema of legs.	Generalized edema or anasarca.	Enlarged liver.
Series 1 . . .	11	5	30	61	36	23	27	10	24
Series 2 . . .	1	1	7	12	18	4	10	..	10
	—	—	—	—	—	—	—	—	—
Total . . .	12	6	37	73	54	27	37	10	34

TABLE 7.—CARDIAC PHYSICAL SIGNS AND HEMIPLEGIA.

Number cases.	Mitral systolic murmur.	Presystolic murmur.	Mitral double.	Aortic systolic murmur.	Aortic diastolic.	Thrill.	Pulmonary systolic.	Pericardial friction.	Hemiplegia.
Series 1 . . .	25	3	3	8	5	1	2	3	10
Series 2 . . .	3	1	1	4	4	1	..	2	5
	—	—	—	—	—	—	—	—	—
Total . . .	28	4	4	12	9	2	2	5	15

TABLE 8.—ARRHYTHMIAS.

Number cases.	Pulsus Alternans.	Gallop rhythm.	Auricular fibrillation.	Auricular flutter.	Extrasystole.	Right bundle branch block.	Left bundle branch block.
Series 1 . . .	3	1	12	1	4	1	1
Series 2 . . .			1		5		
	—	—	—	—	—	—	—
Total . . .	3	1	13	1	9	1	1

Thus, dyspnea was by far the most frequent symptoms complained of, the next most frequent being precordial pain. Of the physical signs, those due to congestive failure were predominant: impairment or râles at the bases of the lungs, edema of the legs, enlarged liver, cyanosis. Of the valvular signs, mitral systolic murmurs were found

twice as frequently as any other murmurs, aortic systolic coming second. Auricular fibrillation was by far the most frequent of the arrhythmias, with extrasystole next.

In an analysis of the blood pressure of Series 2, the usual single reading on first examination had to be taken as a basis. No significant results became evident. Of 30 males, 12 had systolic pressures of more than 145 mm. Hg (average, 174; extremes, 228 and 145); the diastolic average for this group was 99 mm. (extremes 146 and 70). Of the 18 men with systolic pressures under 145, the average was 115 (extremes of 140 and 80). The diastolic average of this group was 73 (range, 105 to 40). Ten of 17 females had a systolic pressure above 145 mm. Hg (average of 208; extremes, 300 and 160). Their diastolic average was 118 (extremes, 180 and 80). Females with systolic blood pressure under 145 showed: average systolic pressure, 128 (extremes 140 and 100); diastolic average, 81 (extremes 90 and 70). It is evident that the blood pressure was decidedly higher in the female group than in the male, not only as a group but individually.

Correlation of Body Weight, Surface Area and Heart Weight. Difficulty was encountered in evaluating the end results, since death in both series was due to many different causes, including cases of malignancy with accompanying loss of weight. In a study of 1000 normal hearts by Smith,² the weight of the normal adult heart was found to be 294 gm. for males and 250 gm. for females, with a definite correlation between the weight of the heart and that of the body. The ratio was 0.43% for males and for females, 0.4%. Heart weight increased with body weight, both absolutely and relatively; but with increase of age, the heart remained the same, provided the body weight also was stationary. Children were not included.

In the present study, data existed for 147 cases of Series 1 and 40 of Series 2. There were 95 males and 52 females in the first series, and 25 males and 15 females in the second. The average ratio of heart weight to body weight for both sexes and both series was 0.7% (being 0.7% for both males and females). Of the 120 males in the two series, the ratio of heart to body weight was normal (using the 0.43% of Smith), in only 3 cases (2.5%); below normal were 8 (6.7%), the lowest being 0.25%, while 109 (90.8% of the cases) were higher than 0.43%, distributed as follows:

Ratios, per cent.	Average, per cent.	Number cases.
0.44 to 0.52	0.48	25
0.53 to 0.62	0.59	21
0.63 to 0.72	0.66	17
0.73 to 0.82	0.74	20
0.83 to 0.92	0.86	8
0.93 to 1.02	0.95	11
1.03 to 1.12	1.07	4
1.13 to 1.22	1.15	2
1.23 to 1.32	1.26	1

In the two series there were 67 females whose ratio of heart weight to total weight was studied. In 6 cases, the ratio was lower than 0.4% (Smith's average normal), the lowest being 0.27%. The great majority (91%) was above 0.4%, as follows:

Ratios, per cent.	Average, per cent.	Number cases.
0.41	0.41	2
0.41 to 0.43	0.42	5
0.44 to 0.52	0.48	10
0.53 to 0.62	0.59	10
0.63 to 0.72	0.66	10
0.73 to 0.82	0.78	7
0.83 to 0.92	0.88	12
0.93 to 1.02	0.94	1
1.03 to 1.12	1.07	3
1.13 to 1.22	1.14	2
1.23 to 1.32	1.23	0
1.33 to 1.42	1.40	1

Of the 242 cases of this study, the weight of the heart was available in 227. The largest heart weighed 860 gm., the smallest, 170 (average 399). There were 149 males with an average weight of 417 gm., or 123 gm. above the normal (Smith), which is an average 42% increase; of these, the largest heart weighed 860 gm., the smallest, 270 gm. There were 78 females with an average heart weight of 387 gm., an increase of 137 gm. (55%) over normal. The largest was 800 gm., the smallest, 170 gm. The weights were grouped as follows:

Weight (grams). Males.	Average, grams.	Number cases.
Under 290	246	21
290 (normal, 294)	290	3
300 to 349	312	25
350 to 399	365	21
400 to 449	412	21
450 to 499	454	15
500 to 549	525	16
550 to 599	567	8
600 to 649	614	7
650 to 699	650	6
700 to 749	728	2
780	780	1
Over 800	828	3
Females.		
Under 250	217	10
250 (normal)	250	3
250 to 299	277	9
300 to 349	313	15
350 to 399	367	12
400 to 449	416	12
450 to 499	478	4
500 to 549	517	3
600 to 649	610	2
650 to 699	678	5
720	720	1
780	780	1
800	800	1

A study was made of the correlation of surface area, heart weight and ratio of heart weight to body weight. This was possible in the cases of 116 males and 59 females, or 175 of the cases, and is tabulated below:

Surface area in square meters.	Heart weight in grams.	Ratio, heart to body weight, per cent.	Number cases.
Males.			
1.30	275	0.72	4
1.40 to 1.59	349	0.71	21
1.60 to 1.79	403	0.68	44
1.80 to 1.99	468	0.65	36
2.00 to 2.19	559	0.66	8
2.30	355	0.28	1
Females.			
1.10	170	0.59	1
1.20 to 1.39	267	0.71	7
1.40 to 1.59	367	0.77	16
1.60 to 1.79	424	0.59	25
1.80 to 1.99	395	0.51	7
2.00	250	0.27	1
2.00	380	0.45	1
2.20	380	0.36	1

These findings again disclose interesting information. Of 4 males with a heart weight of 275 gm. (below normal) with a surface area of 1.3 square meters, there is still a ratio of 0.72%, higher than the Smith normal (0.43%). The same holds true for 1 female whose heart weight was 170 gm. with a surface area of 1.1 square meters and whose ratio of heart to body weight was 0.59% (normal 0.40%). There was another female with a normal heart weight of 250 gm., but with a surface area of 2 square meters whose ratio of heart weight to body weight was 0.27%, much below normal. Another whose heart weighed 380 gm., 130 above normal, but with a surface area of 2.2 square meters, gave a ratio of 0.36%. These last 2 cases recall the work of Smith and Willius,³ and their statement, "This discrepancy may be responsible for the apparent circulatory inadequacy found in obese persons." The remaining cases showed a definite increase not only of heart weight but also an increase in ratio of heart to body weight.

Discussion. It is well known that changes in the coronary arteries start shortly after birth, consisting of splitting of the lamella elastica interna with the appearance of muscle elements between the two layers. It has also been shown⁴ that these are the beginning of a series of changes that take place as the normal, healthy individual advances in years. This tendency, starting very early towards definite changes in the components of the vessel wall, makes it difficult at times to decide where the process ceases to be normal and becomes pathologic. However, since coronary arteries with normal intimal changes and with mild arteriosclerosis are comparatively free of clinical symptoms, this differentiation is not of great practical moment. This statement cannot be made too

lightly, since an apparently normal vessel may have enough sclerotic changes at the opening of the small branches to give definite symptoms.⁵

In this series, 22 of the 24 cases complaining of pain referable to the heart showed marked sclerosis and only 2 showed moderate sclerosis. None with mild sclerosis gave any history of pain. With these findings, one certainly is more inclined to believe with Sutton⁶ that cardiac pain is closely related to the anoxemia of ischemia of the heart muscle. It is not clear whether this is brought about by greater rigidity of the vessel wall only or by narrowing of the lumen as well. When vessels are injected at normal pressure immediately postmortem with hardening material, it is found that even in cases of sclerosis, the lumen may not be encroached upon.⁷

The general knowledge that arteriosclerosis of the coronary arteries seems to be more prevalent in males than in females is brought out in this study, where 64.5% were males and 35.5% females. It also confirms the known fact that the anterior descending branch of the left coronary is more involved in the process than other branches. Of more unexpected interest was the finding that in this series the left circumflex was more uniformly "markedly" involved (33 times) than any other artery.

Of the clinical signs and symptoms, next to dyspnea pain was the most frequent symptom complained of. Signs of congestive heart failure predominated. Of the arrhythmias, next to auricular fibrillation, extrasystoles were the most frequent. One wonders whether they might not be produced in many cases by irritating foci, the result of arteriosclerosis of small branches, such as found by Sutton and Brandes⁵ on careful histologic study. Mitral systolic murmur, the most frequently found murmur, was probably due in most cases to dilatation of the mitral ring.

These clinical findings agree with those recently published by Fahr⁸ in his study of hypertensive hearts. However, the similarity may be due to the fact that 90% of hypertensive hearts show decided evidence of coronary sclerosis. This brings one to the consideration of the relation of heart weight to body weight. The heart weight was relatively increased in the great majority of both males (90.8%) and females (91.3%). This increase of ratio was not due in all of the 90+% of the cases to an increase in the mass of the heart, since many were afflicted with chronic diseases, such as cancer, with an accompanying loss of weight. However, study of the actual weight of the heart in 233 cases showed that only 16.1% of the males had hearts whose weights were normal or below; and 83.9% had decidedly increased heart weights; only 16.7% of the females had normal or lower heart weight, and 83.3% were above normal. These males and females had an almost identical per cent of increased mass, so that one may conclude that in the great majority of hearts with arteriosclerotic changes in the coronaries, there is an increase in the

mass of the heart. It is probably due to an increase in the arterial pressure in the pulmonary or systemic circulation, or in both. Unfortunately, the blood pressure readings in these cases are of little value, as many were taken in stages of decompensation and do not throw light on a study of this nature.

Conclusion. Study was made of 242 consecutive cases with hearts whose coronary arteries were found postmortem to be sclerotic. There were 156 males (64.5%) and 86 females (35.5%).

History of pain of cardiac origin was given in 14.9% of the cases, of which 24 were males and 13 females; 91.7% of these were associated with marked sclerosis and 8.3% with moderate sclerosis. No cases with mild sclerosis gave a history of pain.

Dyspnea and cardiac pain were the symptoms most frequently encountered. Signs of congestive heart failure were also predominant; of the arrhythmias, auricular fibrillation was the most common, and extrasystole frequent.

The anterior descending branch of the left coronary artery was the most frequent to be "markedly" involved in the sclerotic process (18 times).

Of arteriosclerosis in other organs, the kidneys and spleen were more markedly attacked. Other organs were involved in varying degrees, showing that visceral arteriosclerosis tends to be generalized, although usually affecting the vessels of some organs more than others.

The ratio of heart weight to body weight was found to be increased in 90.8% of the males and 91.3% of the females. The average heart weight in 149 males was 417 gm. or 123 gm. (42%) above normal. Of these, 84% weighed more than normal. Of 78 females, the average weight was 387 gm., or 137 gm. (55%) above normal, 83.3% showed definite increase of heart weight.

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ADEQUATE DOSAGE IN THE SPECIFIC SERUM TREATMENT OF PNEUMOCOCCUS TYPE I PNEUMONIA.*

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WITH the recognition of the beneficial effects of specific antiserum in the treatment of pneumococcus Type I pneumonia and the great increase in the use of this serum since it became available in the concentrated form, it becomes desirable to attempt a definition of the effective dose of this important therapeutic agent. The obstacles which have confronted the various workers in their recent attempts to arrive at uniform standards for measuring the potency of anti-pneumococcic sera¹⁻⁴ have made it difficult to interpret the dosage recommended by most writers.⁵⁻⁸ The realization of these difficulties has resulted in the adoption of values for the units of antibody in Types I and II antipneumococcus sera which are defined in terms of an acceptable standard serum.^{4,9} The use of this standard serum coupled with the adoption of uniform methods of titration tends to fix the value of the unit within fairly narrow limits. It is desirable to know the effective dose of serum expressed in terms of such standardized units. For that purpose, the experiences with antibody treatment of the Type I cases at this hospital are here reviewed. The data with regard to the cases of pneumococcus Type II pneumonia are discussed elsewhere.¹⁰

Clinical Material and Serum Used. The data to be presented are based on a series of 219 cases of pneumococcus Type I pneumonia treated with serum on the medical wards (which admit only patients over 12 years) between November, 1929, and May, 1935, inclusive. The sera used were concentrated and supplied by Dr. L. D. Felton of the Department of Preventive Medicine and Hygiene, Harvard Medical School, and by Drs. B. White, E. S. Robinson, and L. A. Barnes, of the Massachusetts Department of Public Health. We are further indebted to Drs. L. D. Felton and L. A. Barnes for data regarding the titrations of the various lots of serum used, including the standards with which they were compared. These data permitted a revaluation of the dose of antibody used in each patient to make it comparable with the definition of the unit now in use, namely, the protective action of 1/300 cc. of the National Institute of Health's standard serum P11. The lots of serum used varied in

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potency from 600 to 5000 units per cc., the amounts used in each patient varying from 5 to 340 cc., or from 4000 to 1,700,000 units.

The gross death rate in all the cases receiving serum, regardless of amount or time of administration, was 18%, as compared with 39% deaths among 290 contemporaneous cases diagnosed pneumococcus Type I pneumonia during life but, for various reasons, not treated with serum (Table 1). The average amounts of serum used for each case are also shown in this table. The death rate, incidence of bacteremia, and average amounts of antibody are shown for each year in Table 2. It is apparent that these factors alone do not fully explain the differences in results observed from year to year.

TABLE 1.—DEATH RATES IN PNEUMOCOCCUS TYPE I PNEUMONIA AND AVERAGE AMOUNTS OF ANTIBODY GIVEN.

(Boston City Hospital, November, 1929, through May, 1935.)

Blood culture.	Non-serum treated.			Treated with Type I concentrated antibody.				
	Number.	Died.	Per cent.	Average amount antibodies.		Number.	Died.	Per cent.
				Volume (cc.).	Units (× 1000).			
Positive . . .	100	81	81	116	202	69	25	36
Negative . . .	129	24	19	85	123	123	15	12
Not done . . .	60	8	13	74	112	27	0	0.
All cases . . .	289	113	39	94	147	219	40	18

TABLE 2.—ANNUAL DEATH RATES, INCIDENCE OF BACTEREMIA, AND AVERAGE AMOUNTS OF ANTIBODY GIVEN EACH YEAR IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Year.	Non-serum treated.			Treated with concentrated antibody.					Percent of cases with positive blood cultures.	
	Number of patients.	Number died.	Per cent died.	Average amount of antibody per patient.		Number of patients.	Number died.	Per cent died.	Non-serum treated.	Serum treated.
				Volume (cc.).	Units (× 1000).					
1929-30 . . .	49	18	37	122	223	32	7	22	37	26
1930-31 . . .	39	12	31	138	242	39	9	23	45	54
1931-32 . . .	30	9	30	69	77	26	2	8	47	42
1932-33 . . .	48	20	42	93	135	34	5	15	51	33
1933-34 . . .	55	26	47	80	101	42	6	14	39	18
1934-35 . . .	68	28	41	66	102	46	11	24	45	40
1929-35 . . .	289	113	39	94	147	219	40	18	44	37

During the period when these patients were treated, various criteria were used to determine the initial dose of serum prescribed for each patient.^{8,11,12} In general, this dose was based on volume, without due regard to antibody content, and was given in 2 to 5 intravenous injections at intervals of 2 hours. In order to minimize the occurrence of untoward reactions, a small initial injection

(usually 5 cc.) was given and this was followed by increasing amounts up to 40 or 50 cc. In patients who were not adequately improved, further doses were usually given after a lapse of 12 hours or more, the amount and frequency being gauged by the response to the earlier injections. In other patients, who seemed sufficiently improved before the time set for the final injections, the treatment was discontinued. It was usually intended to give serum only to patients in whom the first injection could be made within 96 hours of the onset of the pneumonia. A number of cases, however, were treated later in the disease due to a variety of circumstances.

In order to draw any conclusions with regard to the range of dosage which was therapeutically effective without being unduly redundant, it was necessary to analyze the effects of serum in these cases with respect to: (1) The day of illness when serum was first given; (2) the results of the blood cultures taken before treatment was begun; and (3) the efficacy of various amounts of antibody. Cases were considered therapeutic failures if the outcome was fatal or if crisis or lysis occurred later than the second day after serum treatment was begun. These therapeutic failures will be reviewed, in turn, in an attempt to determine to what extent factors, other than inadequate amounts of serum, were operating against the full efficacy of the specific antibody.

Importance of the Day of the Disease When Treatment is Begun. There are differences of opinion among physicians experienced in the serum therapy of pneumococcus Type I pneumonia with regard to the efficacy of this form of treatment when it is begun late in the disease. This lack of unanimity is found in the discussions regarding the use of both the unconcentrated^{5,13} and the concentrated serums.^{7,8,14} The comparatively less striking effects on the death rates and the difficulty of interpreting the clinical results when treatment is instituted late in the disease has led recent workers conducting large scale therapeutic experiments in this country¹⁵ and in Great Britain¹⁶ to limit this therapy, somewhat arbitrarily, to patients in whom it can be instituted within the first 4 or 5 days of the disease.

The numbers of cases treated on different days are listed in Table 3 according to the day when antibody was first given. Day 1 represents the calendar day of the initial chill or chest pain, whichever occurred first. Almost all of the cases listed as treated on the fifth day received their first injection of serum within 12 hours of the 96-hour period usually designated as the limit for treatment. It is to be kept in mind that, although the total number of cases seems adequate, the numbers become quite small when subdivided into the various categories under consideration. Any deductions made, therefore, are subject to this reservation and are necessarily based only on the general trend of the results.

TABLE 3.—INFLUENCE OF THE DURATION OF THE DISEASE AT THE TIME ANTIBODY IS FIRST ADMINISTERED ON THE OUTCOME IN CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Day treatment begun.	Blood culture positive.						Blood culture sterile or not done.					
	Number of cases.	Died.	Per cent died.	Recovered.*			Number of cases.	Died.	Per cent died.	Recovered.*		
				By crisis or lysis within.		Empyema.				By crisis or lysis within.		Empyema.
				2 days.	3 or more days.					2 days.	3 or more days.	
First or second . . .	5	1	20	3	1	0	14	1	7	9	4	1
Third . . .	16	5	31	9	2	1	34	2	6	31	1	0
Fourth . . .	16	5	31	5	6	2	47	3	6	39	5	0
Fifth . . .	12	3	25	5	4	6	25	2	8	18	5	0
Sixth . . .	6	3	50	3	0	1	15	3	20	10	2	2
Seventh or later . . .	14	8	57	2	4	0	15	4	27	7	4	2
Fifth day or earlier . . .	49	14	29	22	13	9	120	8	7	97	15	1
Sixth day or later . . .	20	11	55	5	4	1	30	7	23	17	6	4

* Cases with empyema are listed twice. Where the date of termination of the pneumonia was indefinite, the cases are listed as having recovered 3 or more days after treatment.

With respect to death rates, these cases divide themselves sharply into those treated on the fifth day or earlier and those treated on or after the sixth day. The death rates were essentially the same among the cases treated on each of the first 5 days of the disease. There was a sharp increase in the death rate when treatment was begun on the 6th day and a further increase among those treated still later. There was a much greater percentage of deaths among the cases with positive blood cultures, but the influence of the time factor on the death rate was similar in the bacteremic and in the non-bacteremic cases.*

The recovered cases are also of interest. In 97 (87%) of the 112 non-bacteremic patients who were treated on or before the 5th day and recovered, the disease terminated by crisis or lysis within 2 days after the first injection of serum. In fact, only 16 of these 97 cases still had fever and elevated pulse rate on the 2d day after the onset of this therapy. Among the 35 bacteremic patients who were treated on or before the 5th day and recovered, 22 (63%) recovered by crisis or lysis within the first 2 days after receiving serum; 18 of these recovered completely and 4 later developed empyema. Among the cases treated late in the disease, that is, on or after the 6th day, a smaller proportion exhibited a prompt recovery which could be reasonably attributed to serum.

The results in these cases indicate that treatment may be equally effective as a life-saving measure in cases of pneumococcus Type I

* The 27 cases in which blood cultures were not made, 6 of which were treated after the fifth day, are grouped, for the sake of convenience and brevity, together with the cases having sterile blood cultures, since the results in all these cases were very similar (see Table 1). They are here referred to as "non-bacteremic" cases.

pneumonia if begun any time within the first 5 days of the disease. It is difficult to evaluate the results of treatment begun later than the 5th day, due to the increasing number of spontaneous recoveries occurring on or after the 6th day. It would seem, however, that late treatment, particularly if begun on the 6th day, resulted in a lower death rate in bacteremic cases and brought about a more rapid termination of the disease in the recovered non-bacteremic cases.

Empyema occurred in only 1 of the 112 recovered non-bacteremic cases, in which treatment was begun on or before the 5th day, an incidence of less than 1%, whereas 4 (17%) of the 23 recovered non-bacteremic cases that were treated on the 6th day or later developed this complication. Among the 35 recovered bacteremic cases who were treated on or before the 5th day, empyema developed in 9 (26%). Up to the 5th day, there was a steady increase in the incidence of empyema proportional to the delay in treatment.

It would appear, therefore, that the administration of antibody almost eliminates the possibility of empyema developing in the non-bacteremic cases, if this treatment is begun on or before the 5th day. It tends to reduce the incidence of this complication appreciably in bacteremic cases if begun on or before the 3d day.

TABLE 4.—EFFICACY OF DIFFERENT AMOUNTS OF SPECIFIC ANTIBODY IN THE TREATMENT OF PNEUMOCOCCUS TYPE I PNEUMONIA.

Blood culture.	Units of antibody. Unit = 1/200 ee. of standard serum F146, or 1/300 ee. of standard serum P11.	Treatment begun on or before the fifth day.						Treatment begun after the fifth day.					
		Number of cases.	Died.	Per cent died.	Recovered.*			Number of cases.	Died.	Per cent died.	Recovered.*		
					By crisis or lysis within.		Empyema.				By crisis or lysis within.		Empyema.
					2 days.	3 or more days.					2 days.	3 or more days.	
Positive	75,000 or less 76,000 to 150,000 151,000 or more	12 16 21	5 5 4	42 31 19	6 6 10	1 5 7	1 2 6	5 4 11.	4 2 5	80 50 45	1 2 1	0 0 5	0 0 1
Negative or not done	50,000 or less 51,000 to 75,000 76,000 to 100,000 101,000 to 150,000 151,000 or more	20 31 12 35 22	0 3 1 1 3	0 10 8 3 14	16 24 11 31 15	4 4 0 3 4	0 1 0 0 0	6 13 11	3 1 3	50 8 27	3 7 7	0 5 1	1 2 1

* See footnote, Table 3.

Relative Efficacy of Various Amounts of Antibody (Table 4). Among the non-bacteremic cases treated on or before the 5th day there was no correlation between the death rate and the number of units of antibody administered. Likewise, in 80% or more of the recovered cases of this group, the disease terminated by crisis or lysis within 2 days after treatment was begun regardless of

whether the dose was large or small. After the 6th day of the disease, however, the larger amounts of serum seemed to influence the disease more favorably than the smaller doses.

There was a smaller proportion of deaths among the bacteremic cases who received the larger amounts of serum. Empyema, however, was more frequent in those that recovered, when the larger doses were used. This may be accounted for, at least in part, by the fact that serum therapy was continued in such cases due to the persistence of fever and symptoms.

The distribution of cases and deaths according to the amounts of antibody given at different stages of the disease is shown roughly in Table 5. Larger doses were used more frequently in cases where the treatment was begun late in the disease. These large doses were more effective in saving life, however, in the cases where they were used early.

TABLE 5.—DISTRIBUTION OF CASES AND DEATHS ACCORDING TO THE TOTAL AMOUNT OF ANTIBODY GIVEN AND THE DAY OF ILLNESS WHEN TREATMENT WAS BEGUN.

Time treatment begun.	Blood culture positive.				Blood culture sterile or not done.			
	75,000 units or less	76,000 to 150,000 units.	151,000 units or more.	Total.	75,000 units or less.	76,000 to 150,000 units.	151,000 units or more.	Total.
	2*	2	2	6	1	1	1	3
Third day or before	5	9	7	21	20	18	10	48
	3	3	2	8	3	1	2	6
Fourth or fifth day	7	7	14	28	32	28	12	72
	4	2	5	11	3	1	3	7
Sixth day	5	4	11	20	6	12	12	30
	9	7	9	25	7	3	6	16
Total	17	20	32	69	58	58	34	150

* The superscripts represent the number of deaths.

In order to arrive at any reasonable conclusion with regard to what is the optimum dose of antibody, it is necessary further to determine for the individual cases: (1) Whether insufficient dosage could account for the therapeutic failures; (2) whether other factors were operative which could account for the poor responses; and (3) to what extent the larger doses could be considered redundant. It may suffice to consider, in some detail, only those cases which might be considered therapeutic failures. Almost all of the cases in which crisis or lysis took place within 2 days received only the dose originally prescribed for them on the basis of volume. The larger doses used in these cases resulted from the fact that more potent lots of serum were available at the time and, therefore, such doses may have been redundant. In the cases that died after a lapse of 2 or more days and in those cases in which the crisis or lysis was delayed for more than 2 days, additional antibody was usually given, but with no regularity. In a few of the cases the

doses were regulated on the basis of the absence of agglutinins in the blood.¹² The essential features of the fatal cases and those with delayed crisis are summarized in Tables 6, 7 and 8.

Poor Responses Among Non-bacteremic Cases in Which Serum Treatment Was Begun On or Before the Fifth Day (Table 6).

There were 14 cases among the 23 of this group in which a total of 75,000 units or more of antibody was given. Four of these cases had definite complications which were diagnosed and which could adequately explain the fatal outcome or the delayed improvement, namely, hemolytic streptococcal infections of the respiratory tract in Cases 2 and 5, an infected abortion in Case 23 and cardiac failure with auricular fibrillation in Case 22. There were 2 further instances, Cases 3 and 19, in which the difficulty and irregularity with which the Type I pneumococci were found suggested that some other cause or infecting agent was operative, but was not identified. In these 2 cases it is likely that the Type I pneumococcus infection, if present before serum treatment was begun, may not have been an important factor in the latter part of the illness.

Four cases in which the larger doses were used had either an entire lung consolidated (Cases 4 and 15) or bilateral lung involvement (Cases 16 and 18) at the time that serum treatment was instituted. Together with Case 11, in which 72,000 units were given, and Cases 7 and 23, which are also mentioned in other connections, these were the only cases in the group under consideration in which such extensive involvement was noted before serum treatment. Even 120,000 units were still inadequate in such cases, as judged from the results in Cases 4, 16 and 18.

In Cases 12 and 21, the initial dose of 104,000 and 96,000 units, respectively, was followed, in each instance, by what appeared to be a crisis. On the second day following this improvement there was a recurrence of fever without respiratory distress, toxemia or appreciable elevation of the pulse rate. Additional amounts of antibody were given in these cases because the temperature rose to 101° F., and the fever subsided promptly thereafter. In the 2 remaining instances in which 75,000 units or more were used (Cases 7 and 17) this dose was spread over 2 or more days.

In the 9 remaining cases, less than 75,000 units of Type I antibody were used. Except for Case 8, in which the date of onset may be questioned, the poor response in these cases may reasonably be ascribed to insufficient dosage or to doses spread over intervals that were too long. In Case 11, already mentioned, the extent of lung involvement was an additional factor in the poor response.

It thus appears that in non-bacteremic cases in which treatment is begun on or before the 5th day of illness doses in excess of 75,000 units are necessary only when the pulmonary lesion has extended beyond the confines of one lobe at the time of the first injection. When larger amounts were used in cases with a single lobe involved, the additional antibody probably served no useful purpose. These further amounts were occasioned by the failure to observe a clinical crisis because of: (1) The presence or probable presence of other infections; (2) the occurrence of slight fever similar to that observed after spontaneous crisis; or (3) the spread of dosage over 2 or more days.

Doses of less than 75,000 units are probably adequate in many non-bacteremic cases treated early, as can be seen from Table 4. In

TABLE 6.—NON-BACTEREMIC CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA SHOWING POOR RESPONSE TO SERUM TREATMENT BEGUN ON OR BEFORE FIFTH DAY OF ILLNESS.

Case.	Age.	Lobes.	Units.	Day of disease.											Remarks.
				2	3	4	5	6	7	8	9	10	11		
1	27	Rl	55	O	O	..	O	L	E	..		
2	21	Ru	112	O ²⁵ O ¹¹²	20	10	L	Onset after sore throat; sputum = S.H. and no Pn after 3d day; otitis media = S.H. Ext. Ru; small hemoptyses; rare I in sputum; cultures unsatisfactory.	
3	43	Rl	168	O	PsC	O	..	L		
4	51	Lul	240	O	..	O	L		
5	50	Rl	230	O ¹²⁰ O ²³⁰	O	..	D	Sputum 4th day = S.H. (no Pn).	
6	21	Rl	40	..	O	20	20	Asthma and bronchitis.	
7	57	Rml	90	..	O	O	..	O	D,O	Ext. Ll; bilateral effusion and pulmonary tuberculosis at autopsy.	
8	44	Rl	54	..	O,D	Moribund; delirium tremens; history unreliable; died in 4 hours.	
9	22	Ll	35	O	..	O	L		
10	46	Ll	55	..	O	O	O	O,L	Subcutaneous abscesses during convalescence.	
11	26	Lul	72	O	L	Rheumatic heart disease.	
12	40	Ll	152	O	PsC	Fever without symptoms on 6th day.	
13	35	Ll	48	..	O	O	PsC	..	O	C	15th day	Onset with atelectasis 1 day postpartum; Ext. Lu; sterile pleural effusion. Lung culture 7th day = I.	
14	57	Ll	57	O	..	O	D		
15	75	Ruml	75	..	O	L?	..	D	15th day		
16	23	RILL	120	O	D	Jaundice (icter. index = 25); died in 12 hours.	
17	22	Ll	75	O	L		
18	25	RmlLl	113	O	O,O	L	..	Acute alcoholism; Ext. Ru.	
19	36	Rl	834	..	O	O	..	O	O,L	Meningismus; Pn I obtained irregularly.	
20	40	Rl	27	O	C		
21	36	Ll	144	PsC	..	C	No blood cultures.	
22	76	Rl	163	O	D	Auricular fibrillation; died in 21 hours.	
23	30	Rum	195	O	D	Blood cultures: 8th day = M. tetragenus; 10th day = Staph. albus; abortion of 5-month fetus on 8th day.	

EXPLANATION OF TABLES 6, 7 AND 8.

Lobes = Lung involved at time treatment begun: Ru = right upper lobe, Rml = right middle and lower lobes; Lul = left upper and lower lobes, etc.

Units = Total amount of antibody in thousands (unit = 1/300 cc. standard serum P11 or 1/200 cc. standard serum F146).

Day of Disease = For each case: upper line gives the result of blood cultures and the termination of disease; lower line gives amount of antibody in thousands of units. O = sterile; I = positive for pneumococcus Type I; C = crisis; L = lysis; D = died; E = empyema; PsC = pseudocrisis.

Other abbreviations: Pn = pneumococcus (type indicated by Roman numeral); S.H. = hemolytic streptococcus; P.M. = postmortem; Ext. = extension of pulmonary process; B.M.C. = Bacillus mucosus capsulatus.

many instances, however, these small total doses prove inadequate to produce a rapid and complete response, particularly when they are given over a period of 2 or more days. It seems reasonable, therefore, to deduce that a total dose of 75,000 units is adequate without being redundant if: (1) It is given within a period of a few hours; (2) the treatment is begun on or before the 5th day; (3) the blood culture is sterile before the first injection of serum; and (4) the pulmonary process has not extended contralaterally or to involve an entire lung. When the pulmonary lesion has spread, doses of 150,000 units or more may be necessary and need to be given within a short period to obtain the greatest benefit. When these conditions are fulfilled and crisis is delayed for more than 2 days, other causes should be sought to explain the persistence of fever and symptoms.

Poor Responses Among Bacteremic Cases in Which Antibody Was Given On or Before the Fifth Day (Table 7). It is reasonable to expect that the presence of bacteremia should necessitate the use of large amounts of antibody to bring about an adequate therapeutic response. It is in such patients that Cole demonstrated that the blood serum is capable of neutralizing the protective antibody in antipneumococcus serum.¹⁷ It should be kept in mind that, for purposes of gauging dosage, the blood culture should be taken just before the first dose of antibody is given. The presence of bacteremia may be missed: (1) If one relies on the results of culture taken 1 or more days previously, as illustrated in Cases 27, 29, 31, 37 and 42; or (2) if one depends on the results of cultures taken after some injections of antibody, as in Cases 30, 31 and 45; or (3) after some non-specific injections¹⁸ have already been given, as in Case 37. In patients with low-grade bacteremia, sterile blood cultures can be obtained for several hours after the intravenous injections of hypertonic glucose or other solutions.¹⁹ Furthermore, the amount of antibody necessary to render the blood stream of bacteremic cases of Type I pneumonia free of pneumococci varies widely. This can be accomplished with less than 30,000 units, as in Cases 30, 31 and 34, or it may require much larger doses, as in Case 46. In some instances, repeated injections of 25,000 to 100,000 units per day, or even huge doses of over half a million units, may fail to accomplish this result, as noted in Cases 25 and 40, respectively.

Among the 27 bacteremic cases under consideration who died or failed to improve promptly after treatment with antibody, 12 received 150,000 units or more. In 7 of these, more than 1 lobe was involved, including: 4 in which the dose was spread over 2 or more days, less than 100,000 units having been given during the first day of treatment (Cases 35, 36, 45 and 47); 1 in which the presence of empyema may have obscured the beneficial effects of serum (Case 39); 1 that was complicated by the occurrence of a miscarriage (Case 41); and another (Case 37) complicated by the development of a septic parotitis. In the 5 remaining cases in which the large

amounts of antibody were used, the dose was spread over a period of 2 or more days in 2 instances (Cases 25 and 33); recovery was obscured by the presence of empyema in 1 (Case 28); and in the 4th (Case 29) there was apparently no improvement in the Type I pneumococcal infection and, in addition, there were complicating urinary and intestinal infections and a mixed infection with Friedländer's bacillus in the lungs. In Case 40, the bacteremia was uninfluenced by 915,000 units given over a period of

TABLE 7.—BACTEREMIC CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA SHOWING A POOR RESPONSE TO TREATMENT WITH SERUM BEGUN ON OR BEFORE THE FIFTH DAY OF ILLNESS.

Case	Age.	Lobes.	Units.	Day of disease.											Remarks.
				1	2	3	4	5	6	7	8	9	10	11	
24	45	Rl	112	..	I	..	O	..	O,C	
25	44	Rl	336	..	I	40	72	48	I	I,I	D,I	Acute alcoholism; liver cirrhosis; Ext. RuLi.
26	50	Rml	135	24	72	48	O,L	O	Jaundice (ict. index = 50).
27	35	Rl	147	O	75	30	O	L	Pregnant 5 months.
28	32	Rl	216	..	I	..	60	87	O	O	..	E	
29	74	Lu	165	O	161	55	I	D	P.M.: pyelonephritis; colitis; B.M.C. and I from lung culture.
30	34	Rl	55	..	I	O*	O	O	O	D	*After initial dose of serum.
31	30	Rl	65	..	O	..	35	30	O	O,L	O	D	20th day	..	B.C. = S.H. on 17th day; empyema = S.H.; P.M.: heart's blood = S.H.
32	43	RmLul	144	72	72	D	O	
33	26	Li	150	90	60	D	Leukopenia (W.B.C. = 1750) before death.
34	19	Ru	60	O	C	
35	27	Rum	170	12	24	24	
36	36	Rum	186	75	95	O	L	
37	32	Ruml	1700	..	I	O	..	42	96	48	C	Delirium tremens.
38	42	Rl	105	I	I,I	1,0	O	O	..	L	..	E	Non-specific serum, 70 cc. on 2d day; parotitis 10th day.
39	26	Rml	368	I	..	25	30	20	10	20	..	E	
40	34	Li	915	I	128	..	O	O	L	E	Empyema I first, later S.II.
41	30	Ruml	162	I,I,I	I,D	I	674 colonies per cc. before serum; P.M.: empyema, resolving and organizing pneumonia, left; early Ru.
42	62	Li	128	..	O	I	..	355	360	Miscarriage.
43	39	Ruml	119	I	..	144	O,D	Ext. Lu; B.M.C. and S.II. cultured from all lobes, and I only from Ru at P.M.
44	43	RiLi	06	I	..	96	D,O	Pn III in sputum; died 10 hours after first dose.
45	41	Ruml	174	90	Died 18 hours after first dose.
46	24	Rl	120	I,I	O	..	L	Delirium tremens; phlebitis in 2d week.
47	21	Lul	158	30	90	54	
48	21	Rl	55	I	I	I	15	15	15	E	
49	40	Rl	68	75	Empyema first I, later S.II. and Staph. aureus.
50	55	Lu	30	I	D,I	Acute alcoholism; liver cirrhosis.
				90	68	P.M.: empyema; coronary infarct.

about 30 hours. In this case the autopsy findings indicated that the pleural and pulmonary process must have begun several days before the time alleged by the patient to have marked the onset of his pneumonia. The huge doses used in Cases 37 and 40 were due to the fact that these amounts were prescribed by volume and the lot used was especially potent, containing 5000 units of Type I antibody per cc.

The 15 remaining cases received a total of less than 150,000 units and, in most instances, this dose was spread over 2 or more days. Four of these cases, including 2 in which death occurred within 18 hours after the first dose of serum, had more than 1 lobe involved at the time treatment was begun.

It is not unreasonable to suppose that the dose, in most of these cases, was inadequate or spread over too long an interval to be of maximum benefit. It is impossible, however, to tell what part these two factors played in the development of empyema or the occurrence of superinfections. The fact that these complications are less common when adequate amounts of antibody are given during the first 3 days of the disease suggests that they might be avoided, at least in some instances, by the introduction of a large amount of antibody within a few hours.

From the observations in these cases it seems reasonable to deduce that, in bacteremic cases, a dose of 150,000 units is usually sufficient to bring about an adequate therapeutic result if: (1) Treatment is begun on or before the 5th day; (2) the entire amount is given within about 24 hours; and (3) the pulmonary lesion has not extended beyond the confines of a single lobe at the time when this treatment is begun. More antibody is probably necessary if 2 or more lobes are involved; the exact amount remains undetermined but is probably not far in excess of 200,000 or 250,000 units. It is not unlikely that some cases of empyema and, perhaps, even some instances of superinfection with other organisms might be avoided if antibody is given in this manner.

Poor Responses Among Cases in Which Treatment With Antibody Was Begun After the Fifth Day (Table 8). Of the 50 cases treated on or after the 6th day, 28 (56%) either terminated fatally or failed to improve until 3 or more days after antibody treatment was begun. This is almost twice the frequency with which poor responses were encountered among the cases treated earlier in the disease (50 of 169 cases—30%). This discrepancy occurred in spite of the fact that larger doses of antibody were used more frequently (Table 5) and the average number of units used was 41% more among the cases treated after the fifth day than among those treated earlier (Table 9).

The interpretation of the results of therapy begun on the 6th day or later is difficult because spontaneous recoveries occur with increasing frequency after the 6th day. Among cases treated this late in the disease, some are likely to be *in extremis* and could hardly be expected to benefit from the antibody. In the present series, this occurred 4 times (Cases 53, 54, 70 and 72), and death followed within a few hours in each instance. Other

features, such as (1) massive bacterial invasions as in Cases 51 and 55, (2) mixed infections as in Cases 53, 64, 69, 70 and 78, (3) simple empyema as in Cases 66, 67 and 76, or (4) other focal pneumococcic complications, with or without empyema, as in Cases 59, 60 and 69, all tend to make the demonstration of clear-cut beneficial effects of antibody difficult if it is administered later than the fifth day. In addition to these cases, there were 7 in this series in which the dosage could be considered inadequate

TABLE 8.—CASES OF PNEUMOCOCCUS TYPE I PNEUMONIA SHOWING POOR RESPONSE TO SERUM TREATMENT BEGUN AFTER THE FIFTH DAY.

Case.	Age.	Lobes.	Units.	Day of disease.												Remarks.
				4	5	6	7	8	9	10	11	12	13	14	15	
51	74	Rum	222	I*			D									*1000 colonies per cc.
52	58	Lul	63		222		D									Day of onset doubtful.
53	66	Lu	48		I											Pn X also in sputum and blood.
54	39	RulLi	8		I, D											Rheumatic heart disease; died 6 hours after first dose
55	32	Lul	8				I*	I	D							*2200 colonies per cc.
56	21	Lul	99	O			I			D						
57	33	RILi	1020		O		I		O	O	O, D					
58	52	Rum	765				I	165	255	84	96	O	O	51	O, L	Massive atelectasis of right lung on 12th day—persisted 2 months.
59	37	Lul	190					120	70	E		I	(I 25th day)			Rib resection; Pn I meningitis 30th day.
60	13	Li	264				I	120	48	48	48	D	O			P.M.: interlobar empyema and meningitis (Pn I).
61	22	Ri	216					I		O			C			Miscarriage.
62	41	Li	189		O				I	I	O	I	O, C			Ext. Lu.
63	45	Rum	149		O	I				O		D				Ext. Lul.
64	43	Rum	168							52	88	I, I	*D			*126 colonies Pn I before serum; 2700 colonies Pn III (no Pn I) 13th day; I and III from lung.
65	41	Lul	549								I	I	I	I	I	O, 16th and 17th day; lysis 18th day; sterile pleural effusion.
66	34	Rul	431			O					E					No blood cultures.
67	40	Rum	155			339	69	44								
68	43	Rm	5			155		O, D	I							
69	32	Lul	48		O		D, O									P.M.: empyema (I) and pericarditis (I); Pn III (no Pn I) in Lu.
70	16	Lul	216			O	D									Died in 15 hours; strep. and I in Lu at P.M.
71	44	Li	312			O		D								Sudden death 12 hours after apparent crisis.
72	37	?	37			O, D										Moribund; died in 4 hours.
73	45	Rul	96					48	48		L					No blood cultures.
74	24	Rum	141				O	O, O				L				
75	23	Li	100					O					L			Ext. Lu and Rm.
76	27	Li	144						16	69	24			L		E
77	53	Ri	159						O	O	O		O			O 16th day and 20th day; died 21st day; P.M.: abscess Ri; I from Li; heart's blood sterile.
78	43	All	534						O	O	O	51	35	48	D	No Pn in sputum after 10th day; P.M.: multiple Staph. aureus abscesses (no Pn) in lungs.

even when judged by the criteria mentioned for cases treated earlier in the disease. The blood culture in these cases was positive in 3 (Cases 52, 56 and 63), sterile in 3 (Cases 68, 74 and 75) and not done in 1 (Case 73). There remain only 6 uncomplicated cases who received doses which could be considered adequate for cases treated earlier (Cases 57, 58, 61, 62, 65 and 71). The effect of the antibody in at least 3 of these, namely, Cases 58, 62 and 65, would suggest that much larger doses may be required in bacteremic cases who are treated later than the fifth day than those found to be adequate in similar cases in which treatment is begun on or before the fifth day. In 2 instances, Cases 58 and 62, bacteremia recurred after the blood stream had been temporarily sterilized. In Case 58, 420,000 units had been given before the last positive culture was obtained. The fact that in two-thirds of the cases noted in Table 8 the lesion had extended far beyond the confines of a single lobe at the time treatment was begun would also indicate the need for larger doses in the late cases.

TABLE 9.—COMPARISON OF THE INCIDENCE OF POOR THERAPEUTIC RESPONSES AMONG CASES TREATED BEFORE AND AFTER THE FIFTH DAY OF ILLNESS AND THE AVERAGE AMOUNT OF ANTIBODY USED.

Blood culture.		Cases treated on or before the fifth day.	Cases treated on or after the sixth day.
Positive	Number of cases	49	20
	Deaths or delayed crisis	27	15
	Per cent	55	75
	Average units per case ($\times 1000$)	191	232
Negative or not done	Number of cases	120	30
	Deaths or delayed crisis	23	13
	Per cent	18	43
	Average units per case ($\times 1000$)	109	167

If anything can be deduced from these late cases, therefore, it is the necessity for using larger doses of antibody than those which could be considered adequate in comparable cases treated before the 6th day. This seems to be true even under the most favorable conditions.

Comment. The rapid and dramatic clinical improvement following treatment with concentrated Type I antibody in cases of pneumococcus Type I pneumonia have been noted by many observers,^{7,11} and the regularity with which such a response occurs has been previously reported.⁸ These observations have justified the use of the clinical response to antibody as a guide to dosage and as an indication, when dosage has been adequate, of the presence of complicating factors interfering with the full efficacy of the antibody. In our experience, the commonest causes of the failure to observe this dramatic improvement within 8 to 24 hours after beginning treatment are, in the order of their frequency: (1) Errors in typing; (2) insufficient dosage according to the criteria set down, including dosage spread over too long an interval; (3) the beginning of focal pneumococcic complications; (4) mixed infections in the lungs; or (5) other complicating infections or febrile conditions; and (6) errors in estimating the time of onset of the disease or (7) the extent of the pulmonary lesion.

The following practical procedures are recommended in order to obtain the greatest benefit from antibody treatment: (1) An

attempt should be made to obtain a pneumococcus type as rapidly as possible, by all available methods, *whenever the diagnosis of pneumonia is suspected*; (2) blood cultures in suitable broth media should be made frequently; (3) when a Type I pneumococcus is reported, the date of onset of the pneumonia, that is the exact time of the initial chill or pleuritic pain, and the extent of the pulmonary lesion should be determined by a careful history and physical examination—a roentgenogram should be made, if feasible; (4) a blood culture should be made immediately before giving the first dose, *whether or not previous cultures were made*; (5) serum should be given promptly in the amounts noted in the summary; (6) these doses should be given with the customary precautions in as short an interval as is consistent with the safety and comfort of the patient. With the serums now available a dose of 75,000 units can be obtained in a total volume of 15 to 40 cc. and can be given, without untoward effects, in 2 or 3 doses at intervals of 2 hours or less. Depending on the particular lot of serum, the initial injection may be from 2 to 10 cc., the second may contain from 10 to 20 cc. and subsequent injections of 2 or 3 times the latter volumes may be given safely. If blood cultures are reported positive, the amounts mentioned should be given *regardless of any clinical improvement apparent in the patient*.

If no improvement takes place, or if the degree of improvement seems inadequate in view of the dosage used, then the following procedures may be necessary: (1) The bacteriologic status should be checked to ascertain whether the Type I pneumococcus is present. This means retyping the sputum, preferably from another specimen; (2) wherever possible, a direct culture of the sputum should be made, or other special methods used to determine the presence of mixed infections;²⁰ (3) further blood cultures should be made; (4) the patient should be investigated clinically for the presence of complications.

It may be of interest, in gauging dosage, that the incidence of bacteremia in our cases was found to be increased with advancing age, closely paralleling the death rate. It may, therefore, be desirable to begin treatment with large doses in patients over 40 and particularly in those over 50 years of age. The small numbers of cases preclude an adequate analysis of the influence of age, alcoholism, and other factors in addition to those already considered.

Skin tests with soluble specific substances,^{21,22,23} and agglutination tests in the patients' sera by various techniques^{12,24,25} may prove useful in determining the necessity for further amounts of antibody. The possibilities for the use of these aids have not yet been adequately explored. Our own limited experience warrants certain cautions in interpreting the results of these tests. A positive skin test with Type I soluble specific substance is an indication that sufficient antibody has been given, provided that this test is done 6 hours or more after the last injection of antibody. A negative

skin test, however, may be obtained in many instances when additional doses will serve to no useful purpose, namely, in the presence of complications or of mixed infections. The agglutination of Type I pneumococci by the patient's serum, either microscopically or macroscopically, is an indication of a sufficient excess of antibody only when this agglutination is marked. In certain instances minor degrees of clumping have been observed, particularly with the microscopic methods, before the required dose had been given, and even before the blood stream had been completely sterilized.

Summary and Conclusions. The results of specific therapy in a series of 219 cases of pneumococcus Type I pneumonia treated with concentrated antibody between November, 1929, and May, 1935, were reviewed in an attempt to determine the effective dose of this agent. For this purpose, the doses employed were reduced to values consistent with the definition of the unit of Type I antibody in terms of Felton's standard serum (F146 = 200 units per cc.) and the National Institute of Health's standard serum (P11 = 300 units per cc.).

The optimum dose was determined on the basis of the amount of antibody which brings about a rapid crisis in the largest percentage of cases without being unduly redundant. Due allowance was made for the influence of complicating factors which might mask the beneficial effects of the antibody.

On the basis of the observations in these cases, the following scheme of dosage seems justified for the treatment of uncomplicated cases of pneumococcus Type I pneumonia:

1. In cases in which treatment is begun on or before the 5th day of the disease *and* the blood culture taken before the first injection of serum is sterile *and* the pulmonary lesion is limited to a single lobe, a dose of 75,000 units is adequate provided that this entire amount is given within a few hours.

2. Under the same conditions, but with more extensive pulmonary involvement, 150,000 units should be given in a similar manner.

3. When treatment is begun on or before the 5th day *and the blood culture before the first injection is positive*, a dose of 150,000 units is usually adequate provided that the lesion is still limited to a single lobe; but 200,000 or 250,000 units may be required if the pulmonary lesion has already spread before the treatment is begun. These total amounts of antibody may prove ineffective if their administration is spread over 2 or more days.

4. When treatment is begun after the 5th day of illness, only a small percentage of cases are likely to derive sufficient benefit from the antibody to warrant its use. In these cases, the dose should be much larger than is required in comparable cases treated earlier in the disease.

Empyema may be prevented by early and adequate specific treatment.

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THE BABIES' HOSPITAL OF PHILADELPHIA TWENTY-FIFTH ANNIVERSARY DINNER.

THE Twenty-fifth Anniversary of the foundation of the Babies' Hospital of Philadelphia was celebrated on November 17, 1936, at a dinner at the Barclay Hotel. It was attended by three hundred friends of the institution, and took the form of a memorial in honor of Dr. Charles Andrew Fife, a founder and the first President of the Hospital.



CHARLES ANDREW FIFE, M.D.

Mr. Frederick A. Rakestraw, the President, introduced Mr. Howard A. Loeb as Toastmaster. Dr. John F. Sinclair, Medical Director, also a founder and one of the physicians active in the creation of the Hospital presented an historical sketch of the

modest beginnings of the institution first as a summer hospital at Wynnefield, Pa., followed by the establishing of a Country Hospital at Llanerch, Pa., providing care for sick babies, and fresh air and wholesome food for convalescent babies and children. A city branch was early established to meet the needs of the ambulatory sick, to care for well babies, and to insure a systematic check-up of the health of children discharged from the Country Hospital. *This supervision, by doctors and public health nurses, is continued until they enter the public schools.*

Some time later a large cottage at Beach Haven, N. J., was presented to the Babies' Hospital as a convalescent home for mothers with their children, where they might receive not only good care, but a rest from their arduous duties in their overcrowded homes.

Dr. Sinclair showed, that in a sense, the title of the institution is a misnomer, it is more than a hospital; it is a Health Unit, making itself responsible for the health of all members of the family, maintaining a prenatal clinic and an obstetrical service, providing complete periodic physical examination of all children brought to its attention and offering instructions to mothers in the care of their children. In addition there is a well-equipped hospital floor for acutely ill children who present diagnostic problems and require research and laboratory studies.

Dr. Philip Van Ingen, Director of Pediatric Service of the Roosevelt Hospital, New York, traced the changing conceptions of the care of the young, from the early emphasis on their religious training, to interest in their health, during the pre-school period. Community Health Work among children, which at first restricted itself to providing them with clean milk and medicine in the summer months, has been transformed into a consistent educational effort, coördinated with eternal vigilance throughout the year. In the early days, aside from the prevention of smallpox, little was known about preventive medicine for children, but the work has extended rapidly in all directions. Today it concerns itself with the avoidance of the extravagance of hospitalization by a system of preventive medicine, health supervision and convalescent care, infinitely less expensive and more effective.

Dr. Borden S. Veeder, Professor of Clinical Pediatrics, Washington University School of Medicine, St. Louis, Mo., paid an eloquent tribute to Dr. Fife, based on his life-long personal friendship with him, and his close association in the institution, once

familiarly known in Philadelphia as "Fife's Hospital." As a young practitioner, Dr. Fife was appalled by the terrible mortality among infants in the slums of the city during the summer months and the inadequacy of the facilities for their proper care. Gather-



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ing about him a group of physicians similarly minded, he took the first steps toward remedying this condition, and from then on until his death, the Babies' Hospital became a large part of his life. To this work he devoted himself and the institution became the soul and the heart of the man. His personal gentleness and

patience with sick and spoiled children and with anxious mothers made him eminently successful in his speciality. His Presidential Address before the American Pediatric Society set forth the duties, functions and obligations of the pediatrician in words which established an ideal that he himself attained so far as it is humanly possible.

The Hospital that he founded is no ordinary hospital; it transcends mere hospital care of the sick, and presents the newer and sounder conception of prevention, thereby reducing the need for hospitalization. It is largely due to his efforts and to those of his associates that the days are gone forever when one out of every five babies born to the under-privileged in Philadelphia, die in infancy.

At the conclusion of Dr. Veeder's address, a resolution was offered and adopted, to establish a permanent endowment fund for the Babies' Hospital as a memorial to Dr. Charles Andrew Fife.

BOOK REVIEWS AND NOTICES.

A DOCTOR'S ODYSSEY. A Sentimental Record of Le Roy Crummer: Physician, Author, Bibliophile, Artist in Living, 1872-1934. By A. GAYLORD BEAMAN. With a word in Memory by A. EDWARD NEWTON and Numerous Memoirs and Appreciations. Pp. 340; 21 illustrations. Baltimore: The Johns Hopkins Press, 1935. Price, \$2.50.

THE DOCTOR AND THE PUBLIC. A Study of the Sociology, Economics, Ethics, and Philosophy of Medicine, Based on Medical History. By JAMES PETER WARBASSE, M.D. Pp. 572; illustrated. New York: Paul B. Hoeber, Inc., 1935. Price, \$5.00.

OVER a biographical record frankly labeled "sentimental," as over the official biography and the charity performance, criticism must be, by tradition (perhaps unwarrantedly, since they are all up for sale), discreetly non-committal. Without violating tradition or the allied canons of good taste, the Reviewer, nevertheless, may be permitted in this instance to advise the potential reader of Mr. Beaman's book that he will find this not at all an odyssey in the classic meaning of the term, nor yet such a one of the interior life as emanated some years ago from Paris out of Dublin. Dr. Crummer's life, it would seem from this series of memoirs and appreciations, lacked the usual elements of external conflict and occasional inner incertitude, the triumph over which has constituted from ancient times the most enduring stimulus to literature and the imagination of mankind.

If this was a life deficient in the daily drama of the multitude, in its own more rarefied atmosphere it was colorful and productive. Dr. Crummer achieved in his lifetime an enviable reputation for his versatile accomplishments, not least among these being his bibliophilic studies and discoveries. Indeed, it is not unlikely that these are the achievements by which he will be best remembered in time to come—and it is not improbable that he would wish it so. For the paramount interest of his maturer years seems to have been in these studies. His attitude toward the study of medical history, it should be noted, for all his personal indulgence in the so-called amenities of book-collecting, was a fundamentally sane and irreproachable one. The study of medical history meant to him not an idle hour spent in the reading of medical biographies, but the attempt to trace the continuous stream of medical progress from its beginnings to his own day, to relate its development at a given period to the life of the people of that day. He looked upon it in other words not as a diversion, but as a proper, and even necessary occupation of the intelligent physician. It is the misfortune of this book that its subject too often is made, probably unjustly, to seem to posture gracefully, but meaninglessly, *in vacuo*. It is the wise man, as some one has or should have said, who dictates that his biography shall be written not by his friends but by his enemies.

Dr. Warbasse's book is a more virile illustration of the modern physician's growing tendency to see life (in the sociological sense) and see it whole. The first part of the book is, in respect of outward form at least, a more or less conventional history of medicine; that is, the story is told largely by means of paragraphic biographies interspersed with sections of explanatory background. Beginning with the eighteenth century, however, the emphasis comes more and more to be placed on movements and ideas, on the tracing of the increasing recognition by doctor and public of their interlocked

destinies. The final chapters of the book are devoted to an examination of the various systems of group medicine now in use. It will be no surprise to those familiar with the author's interest in consumers' coöperatives to find him a staunch advocate of the application of similar practices to medicine. The important fact is that Dr. Warbasse's arguments are so well documented—and set forth with so persuasive an enthusiasm—that it would be hard to conceive of any one, doctor or layman, not being stimulated by them to a more vigorous personal interest in the most important political question now confronting the medical profession. But the book is not the work of a brilliant and persuasive doctrinaire. The range of Dr. Warbasse's vision is nowhere better exemplified than in the last section of his book. Here, after nearly 550 pages of emphasis on the necessity for coöperative enterprise between the doctor and the public, he writes movingly of the physician as an individual. "The world envelops him; but, after all, it is the life he lives alone that counts. His real calling is the building of an individual. And that individual is himself—the physician." If history be properly subject to individual interpretation, which indeed is inevitable, this book makes a notable contribution to the contemporary histories of medicine. It is not distinguished for elegance of style or for adding measurably to our factual knowledge. Its virtue is the rather rare one of clothing the familiar and known in a new and more illuminating light; which, after all, is the most acceptable reason for rewriting ancient history.

W. McD., 2d.

PASSIVE VASCULAR EXERCISES AND THE CONSERVATIVE MANAGEMENT OF OBLITERATIVE ARTERIAL DISEASES OF THE EXTREMITIES. By LOUIS G. HERRMANN, A.B., M.D., Assistant Professor of Surgery, College of Medicine of the University of Cincinnati, and the Cincinnati General Hospital, etc. With a Foreword by MONT R. REID, M.D. Pp. 288; 80 illustrations and 4 colored plates. Philadelphia: J. B. Lippincott Company, 1936. Price, \$4.00.

THIS monograph presents in detail the author's views on the rationale and technique of treating peripheral vascular diseases by means of "passive vascular exercises" ("Pavæx therapy"). A historic section includes extensive quotations illustrating earlier efforts to influence blood flow to the extremities by changing environmental pressure. The physiology of peripheral blood flow, diagnostic procedures and conservative therapy in general are discussed briefly.

Diagrams and figures of the "Pavæx Unit" developed by the author are accompanied by complete instructions for its use in treating patients. Discussion of clinical results with "passive vascular exercise" therapy is limited to single examples of each of the main types of organic arterial diseases involving the extremities. The inclusion of more details concerning changes in skin temperature and other objective criteria of improvement would have added much to this section. Likewise, since several hundred patients had received during several years a total of many thousand hours of "Pavæx therapy," statistical tables on immediate results and follow-up data might well have been included. In discussing contraindications to "Pavæx therapy" the author minimizes, more than others would, the danger of spreading infection.

Written with the viewpoint of one interested in conservative treatment the book contains many excellent practical pointers on the possibilities and limitations of conservative therapy. It provides a summary of the experience of one clinic in a relatively new, but rapidly developing, field.

E. L.

ENDOCRINE TUMOURS AND OTHER ESSAYS. By FREDERICK PARKES WEBER, M.A., M.D., F.R.C.P., F.S.A., Senior Physician to the German Hospital, London. Pp. 207. London: H. K. Lewis & Co., Ltd., 1936. Price, 7s 6d.

THIS consists of miscellaneous discourses, in most cases modified reprints of, the author's articles in journals dealing with endocrine tumors; mutations as comes of such diseases as neoplasms and leukemia; congenital-developmental heredity diseases; treatment of constipation; bilious attacks induced by sea air; unilateral asymmetry; hypersplenism; and other subjects. I. Z.

DIE MOLEKULARPATHOLOGIE DER ENTZÜNDUNG. Ihre Bedeutung für das Krankheitsverstehen und Krankheitsheilen. Eine Einführung für Studierende und Ärzte. By PROF. DR. H. SCHADE, Direktor des Institutes für physikochemische Medizin an der Universität Kiel. Pp. 100; 20 illustrations and 18 tables. Leipzig: Theodor Steinkopff, 1935. Price, Rm. 5.50.

THE application of the methods and principles of physical chemistry and of colloid chemistry to biologic problems has been very fruitful. The author of this little monograph on inflammation is well known for his larger work on "Physical Chemistry in Internal Medicine," and for his many excellent contributions to this subject. Inflammation plays so prominent a part in pathology that a summary of its "molecular pathology" is timely and welcome. The well known cardinal signs of inflammation are discussed in terms of physical chemistry; of changes in hydrogen-ion concentration, osmotic variations, localized temperature changes and so forth. At least a beginning is made in a field of great interest. It is to be regretted, however, that the references to the literature are confined to German publications. B. L.

LEHRBUCH DER INNEREN MEDIZIN. VOLS. 1 AND 2. Dritte Umgearbeitete und ergänzte Auflage. By H. ASSMANN, G. V. BERGMANN (mit F. S. TROEBE), H. BOHNENKAMP, R. DOERR, H. EPPINGER, E. GRAFE, FR. HILLER, G. KATSCH, P. MORAWITZ, A. SCHITTENHELM, R. SIEBECK, R. STAEBELIN, W. STEFF, H. STRAUB. Pp., Vol. 1, 934; Vol. 2, 846. Illustrations, Vol. 1, 171; Vol. 2, 153. Berlin: Julius Springer, 1936. Price: paper, Rm. 48; bound, Rm. 52.

THE third edition of this textbook, which came out 2 years after the second, has been somewhat remodeled. Lichtwitz and Thannhauser have been replaced by Assmann, Grafe and Bohnenkamp. A chapter on general hereditary pathology has been added. The general plan of the book, namely, "basing the clinical picture on scientific physiologic-pathologic knowledge, with emphasis on functional disturbances as a starting point of the study of diseases, and thorough consideration of the therapy," has been kept, however. The reader will regret not finding more of the recent studies of pneumococci and filtrable viruses. He will find that the chapter on kidney diseases (Straub) is somewhat old-fashioned, especially as far as the modern clinical methods and the modern concept of the bilateral hematogenous kidney diseases are concerned. The reader will discover also that the chapter on blood diseases (Schittenhelm) contains a number of obvious mistakes: recognition of the long since refuted theory of the origin of the blood cells from ordinary fibroblasts (v. Möllendorff), statements such as that acute hemorrhagic anemia is always hypochromic in nature and that renal anemia occurs in nephroses mainly, and a number of others. In general, it can be said, however, that this edition is as excellent as the former editions, and that it may be strongly recommended to students as well as to medical teachers. W. E.

PROGRESS OF MEDICAL SCIENCE

NEUROLOGY AND PSYCHIATRY

UNDER THE CHARGE OF

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RECENT STUDIES ON ALCOHOL.

Alcohol is the most prevalent of all the noxious materials ingested by man. In view of its predilection for the central nervous system, a review of recent publications concerning alcohol is pertinent to this section. In spite of the prevalence and antiquity of the use of ethyl alcohol both as a beverage and a medicine, it is only recently that our knowledge of the biochemistry and pharmacology of alcohol has been developed to the point where it is comparable to that of other metabolites. Even now we are in ignorance of the intermediary steps in its metabolism in the animal body, and many other aspects of its utilization remain obscure or controversial. However, much interest in the subject has been manifest in the past decade, with the result that certain facts have been established which form a firm foundation for future research.

Alcohol Metabolism. It has been generally accepted since the fundamental work of Mellanby,¹ in 1919, that the ingested alcohol is absorbed as such from the gastro-intestinal tract, and burned by the tissues, the ultimate products being carbon dioxide and water, a relatively unimportant amount, not exceeding 10%, being excreted in the urine, sweat, and expired air. Furthermore, Mellanby showed that this metabolism of alcohol proceeded at a constant rate, irrespective of the concentration in the tissues, since his curves of blood alcohol plotted against time after a single dose were linear in form. This conception was in accord with the observations of subsequent workers, with the exception of Haggard and Greenberg,² who injected alcohol intravenously in dogs and found its rate of disappearance from the blood stream to be proportional to the amount present in the body at the time. Newman and Cutting³ were unable to confirm this finding after intravenous administration in dogs and in man. They also found the same amount of alcohol

to be necessary to maintain the blood alcohol constant at widely varying levels. Thus the preponderance of evidence points to a constant rate of metabolism of alcohol for the individual.

This rate of metabolism is surprisingly resistant to modification. LeBreton⁴ found that raising the metabolic rate of rats 100% by placing them in a cold room did not affect it, nor is violent muscular exercise effective. On the other hand, Widmark⁵ and LeBreton⁶ showed that proteins and amino acids definitely increased the speed of alcohol oxidation. The effect of insulin, dinitrophenol, and carbon dioxide-oxygen inhalation will be dealt with later in connection with therapy of acute alcoholism.

The preponderance of evidence indicates that alcohol may be considered as a food, as it is capable of replacing isodynamic amounts of other foodstuffs. LeBreton⁷ feels that it possesses no specific dynamic action, and has demonstrated that in homeothermic animals it may supply as much as 50% of the basal metabolic requirements, and in poikilothermic animals at low temperatures as much as 90%. She goes so far as to advance the opinion that alcohol may be an intermediary in normal carbohydrate metabolism, a conjecture supported by the constant finding of a small amount of ethyl alcohol in normal blood. Moreover, there seems to be a fairly constant relationship between the basal metabolic rate of different species and their rate of alcohol metabolism.⁸

Mitchell⁹ noted that, when equivalent amounts of alcohol and sucrose were added to the basic diet of two groups of rats, the rats receiving alcohol gained less than those receiving sucrose. On the other hand, the alcohol rats showed a smaller amount of feces, which he interpreted as an indication of superior digestion induced by alcohol.

That the rate of metabolism of alcohol is not increased by muscular exercise is an observation concurred in by Canzanelli, Guild, and Rapport,¹⁰ LeBreton,¹¹ Carpenter,¹² Carpenter, Lee, and Burdett,¹³ and Nyman and Palmlov.¹⁴ From this fact they conclude that alcohol cannot be utilized for muscular work, a deduction that does not seem wholly tenable, since alcohol has a definite and constant rate of metabolism, and the fact that this is not increased by exercise does not prove that no alcohol is utilized in muscular work.

Thus alcohol is seen to replace other foods for most physiologic purposes in approximately isodynamic amounts. That it is a good food does not necessarily follow, as its toxic action must also be considered.

Alcoholism and Deficiency Disease. Alcohol has long been credited with a toxic action on the peripheral nerves, the so-called alcoholic neuritis. Recently much doubt has been cast on the direct responsibility of alcohol for this condition, as well as for "alcoholic pellagra." Strauss¹⁵ treated a number of cases of "alcoholic neuritis" with a high calorie, high vitamin diet, without cutting down on the amount of whiskey they were used to, with the result that the neuritis cleared up in spite of the presence of alcohol. In support of this is the work of Wechsler, Jervis, and Potts,¹⁶ who found no pathologic changes in the nervous system of monkeys and cats habituated to large amounts of alcohol. Thus the present conception is that the neuritis is a deficiency disease, for which the alcohol is only secondarily responsible. This responsibility may be two-fold; in limiting the diet of the alcoholic, and

perhaps in destroying or preventing the absorption of the necessary food factors. Blotner¹⁷ has shown that alcohol is effective in destroying the proteolytic activity of enzymes, lending support to this concept.

Acquired Tolerance to Alcohol. It is generally accepted that certain individuals can tolerate much larger doses of alcohol than can others without exhibiting signs of drunkenness. It is also thought that prolonged and habitual use of alcohol in large amounts is effective in engendering such a tolerance. Because of the great individual variation in non-habituated individuals to alcohol, and the practical impossibility of habituating human subjects for the purpose of experimental study, we have no unimpeachable evidence on this point based on experiments in man, so have had to rely on lower animals for our knowledge. Bogen¹⁸ has recently reviewed the literature concerning this problem, without being able to arrive at any definite conclusion. That acquired tolerance exists seems incontrovertible but its mechanism remains obscure.

Poor absorption of alcohol by the habituated individual cannot be responsible for tolerance, since it has been found by Jungmichel,¹⁹ Fleming and Stotz,^{20,21} Bernhard and Goldberg,²² and Newman and Card²³ that blood alcohol rises faster after ingestion in habituated individuals than in abstainers, indicating more rapid rather than less rapid absorption in these subjects.

Gettler and Freireich²⁴ felt that they demonstrated more rapid oxidation of alcohol in dogs after habituation than in normal controls. The length of time they waited before sacrificing their animals after giving the test dose leaves their work open to criticism; this time averaged little over an hour, during which no great amount of alcohol could possibly have been oxidized. Furthermore, Fleming and Stotz²⁵ and Bernhard and Goldberg²² found no difference in rate of oxidation of alcohol in human habitués and abstainers, and Newman and Cutting^{26,27} showed conclusively in dogs that the rate of alcohol metabolism was not increased by prolonged habituation.

The theory that tolerance to alcohol is a true tissue tolerance is subscribed to by Levy.^{28,29} She found that the minimal anesthetic dose for habituated rats was greater than for abstainers, and that furthermore the alcohol content of the brains of habituated rats was higher than that of abstainers at the same depth of anesthesia. Newman and Card²³ found no difference in the minimal anesthetic dose for habituated and non-habituated dogs, but a definite tolerance of the habituated animals to lower concentrations of alcohol in the blood stream.

Thus, although the last word has not been said regarding the nature of tolerance to ethyl alcohol, it seems that a tissue tolerance rather than decreased absorption or more rapid oxidation is the responsible factor.

Treatment of Acute Alcoholism. There can be no doubt of the desirability of some therapeutic measure which would be effective in expediting the removal of alcohol from the body in acute alcoholic intoxication. Since, as we have seen, but a small amount of alcohol is eliminated by the various excretory systems, and the rate of oxidation of the substance is peculiarly resistant to variation, the problem is a difficult one.

Supniewski,³⁰ in 1926, showed that administration of a large dose of insulin to a rabbit at the same time alcohol was given subcutaneously was effective in almost doubling the rate at which the alcohol disap-

peared from the blood. Almost simultaneously, Widmark,³¹ Serrianni,³² and Newman and Cutting³³ published results showing insulin to be effective in increasing the rate of alcohol metabolism about 50% in dogs and men, when given in doses of from $\frac{1}{2}$ to 1 unit per kilogram. Subsequently, Bickel³⁴ has confirmed these observations. He feels that insulin is effective by lowering the blood sugar, and that if this is prevented no increase occurs. Newman and Cutting³³ obtained a similar effect with insulin-free pancreatic extract, but the fact that Carr, Schmitt, Harne, and Krantz³⁵ found this extract to contain enough insulin to significantly lower blood sugar makes this of doubtful significance.

Harger and Hulpieu,³⁶ Widmark,³⁷ and Newman and Cutting³⁸ have investigated the effect of dinitrophenol on the rate of alcohol metabolism, in the hope that this metabolic stimulant might be effective in burning alcohol. Large doses, exceeding that regarded as relatively safe in man, were effective in more than doubling the rate of fall of blood alcohol in animals. Neymark³⁹ found that the rate of elimination of methyl alcohol, which disappears from the body much slower than ethyl alcohol, could be increased almost five-fold by the drug. This is as would be expected, as Newman and Tainter⁴⁰ found the effect of dinitrophenol on alcohol metabolism to consist solely of an increased elimination of alcohol by the lungs. Since the normal rate of methyl alcohol metabolism is very much slower, the amount of increased elimination by the lungs in its case is more significant than in the case of ethyl alcohol. Using safe therapeutic doses in man, Newman and Cutting³³ could demonstrate no effect on the speed of alcohol metabolism.

In 1924, Hunter and Mudd⁴¹ employed carbon dioxide-oxygen inhalation in the treatment of acute alcoholism. They followed the course of blood alcohol in one subject after a test dose both with and without the administration of the gas mixture, and from this single, apparently rather inconclusive, observation, assumed that the rate of alcohol metabolism was thus increased. In 1926, Van Wulfften Palthe,⁴² arguing from the analogy of symptoms of alcoholic intoxication and oxygen deprivation, administered oxygen to intoxicated rabbits, and reported that they could thus survive ordinarily fatal doses of alcohol. However, Barach⁴³ was unable to confirm this observation. He did find, however, that intoxicated animals in an oxygen deficient atmosphere were improved by inhalation of oxygen, but relapsed on being returned to their former environment. Fleming and Reynolds⁴⁴ were unable to determine any effect on the rate of decline of blood alcohol after administration of either carbon dioxide or oxygen.

In 1935, Robinson and Selesnick⁴⁵ revived the use of carbon dioxide-oxygen therapy, and reported very good results in the clinical course of acute alcoholism after a half hour's inhalation. They further stated that this treatment effected an appreciable decrease in total body alcohol, a deduction to which Newman and Card⁴⁶ took exception. They showed that there was no significant decrease in total body alcohol, either in man or in dogs, after this period of inhalation. They considered the effect to be due entirely to increased elimination of alcohol through the lungs from hyperventilation, and showed that the amount of overbreathing produced by such a mixture of gases for the period of a

half hour was not sufficient to dispose of more than 1% of the alcohol present in the body. That the respiratory stimulation incidental to the administration of the gas might be very beneficial in a patient markedly depressed by alcohol was not denied. However, Selesnick⁴⁷ does not think the number of experiments sufficient for any definite conclusions. Subsequently, Butler⁴⁸ has found oxygen inhalation ineffective in protecting mice from a minimal lethal dose of alcohol, or in improving the condition or behavior of inebriated guinea pigs.

Thus it can be seen that the panacea for acute alcoholism is yet to be found. Dinitrophenol in safe doses is useless. Insulin in large doses is effective in increasing the rate of decline of the blood alcohol about 50%, which probably would not be a significant factor in saving life from the acute toxicity of alcohol, although it might be of use in expediting the "sobering up" process. Carbon dioxide-oxygen inhalation is definitely indicated when alcohol has depressed the respiratory center to a dangerous degree, but cannot be expected to eliminate any significant amount of alcohol from the body.

Chemical Diagnosis of Drunkenness. The extremely dangerous consequences of the operation of modern motor vehicles by drunken drivers has led to the development of more objective tests for inebriety than the traditional "smelling the breath." Within the past 10 years a great deal of work has been done in attempting to correlate the alcohol content of the various body fluids and the breath with the degree of intoxication.

Since the work of Nicloux,⁴⁹ in 1896, there have been many methods introduced for the determination of alcohol. Most of these are based on the oxidation of the alcohol by potassium dichromate, and the subsequent determination from the amount of dichromate used of the amount of alcohol present. Of the modifications recently introduced, that of Friedemann and Klaas⁵⁰ may be recommended for its extreme accuracy, that of Newman⁵¹ for a fair degree of accuracy coupled with rapidity and simplicity, and that of Abels⁵² for its extreme simplicity.

Alcohol determinations have been made on the breath, urine, blood, cerebrospinal fluid, saliva, sweat, and the various bodily tissues. For the determination of drunkenness, each possesses certain advantages and disadvantages. Fresh bladder urine contains approximately the same alcohol concentration as does blood plasma. It is not, however, always easy to obtain, especially without the coöperation of the subject. If it has remained in the bladder for some time, it may correspond better with the concentration of blood alcohol which prevailed several hours previously than with that at the time of examination. Gettler and Freireich⁵³ reported a closer correspondence between spinal fluid and brain than between spinal fluid and blood. However, Melirtens and Newman⁵⁴ showed that during the first hour after taking alcohol the spinal fluid lagged markedly behind the blood alcohol and the clinical signs of intoxication. Furthermore, the difficulty of obtaining it makes it of little value for this work. Breath has the advantage of being easy to secure, but it has been shown that the rate and depth of breathing introduces a variable factor which may lead to large errors. Saliva is easy to obtain, but the possibility of unswallowed alcohol from recent imbibition must be borne in mind. Blood is probably the best from the standpoint of correlation with the degree of

inebriation. However, consent must be obtained for its withdrawal, as one may not be compelled to testify against oneself.

The interpretation of the values obtained is considerably more involved than is their determination. However, with the accumulation of a large amount of data certain generalizations have been made. Turner⁵⁵ states that intoxication is not noticeable when the blood alcohol is under 0.2%, and most other authorities consider 0.2 to 0.25% as the lower limit at which drunkenness may be diagnosed. If the same blood alcohol concentration resulted in the same degree of drunkenness in all individuals the problem would indeed be a simple one, but this is not the case. Individuals vary in their tolerance to the drug, this variation being both inborn and acquired. Thus, although the great majority of individuals may be so inebriated as not to be able to exercise due skill in operating an automobile when their blood alcohol is over 0.25%, certain individuals particularly tolerant to alcohol may not be so affected. As long as these exceptions exist, the chemical diagnosis of drunkenness cannot be absolute, but must be considered only as one bit of evidence among whatever others may be present to substantiate the diagnosis.

Psychopharmacology of Alcohol. The recent interest in the effects of sodium amytal in the psychoses and psychoneuroses, both for prolonged narcosis and to increase the *rapprochement* between physician and patient, has stimulated similar work with alcohol which may lead to a better understanding of the psychological effects of this substance.

The depressant nature of the drug was well demonstrated by Mullin, Kleitman, and Cooperman.⁵⁶ They showed that administration of 60 to 75 cc. of alcohol before retiring decreased the frequency of movements during the first half of the night. During the second half, when most of the alcohol should have undergone metabolism already, there was some increased motility.

In 1930, Perelman⁵⁷ induced light alcoholic intoxication in a group of schizophrenic patients, with resulting development of outbursts of crying and laughing. He felt, however, that he was successful in improving his contact with the patients. Sullivan, in discussion of a paper by Lindemann and Malamud,⁵⁸ reported success in establishing contact with psychotic patients by the use of alcohol. Newman⁵⁹ found that the intravenous injection of alcohol in psychoneurotics produced emotional instability but effected an improvement of contact with the examiner. In a small group of schizophrenics, however, there was a definite withdrawal from reality, with increase in already existing pre-occupations, a marked contrast to the effect of sodium amytal in this condition. Kantorovich and Constantinovich⁶⁰ employed a similar procedure with catatonic patients, and reported good therapeutic results, although a perusal of the data shows a similarity in reaction of most of the cases to that report by Newman.

Thus it would seem that although alcohol is capable of effecting some psychologic change, the change is quantitative and of the nature of an intensification of pre-existing mood, in contrast to the qualitative changes reported with amytal.

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OTO-RHINO-LARYNGOLOGY

UNDER THE CHARGE OF

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RECENT ADVANCES IN THE ENDOSCOPIC ASPECTS OF DISEASES OF THE FOOD AND AIR PASSAGES.

ENDOSCOPY has earned an indispensable position for itself in the diagnosis and treatment of diseases of the upper food and air passages. It is no longer looked upon as a dramatic and spectacular means of removing an alien intruder in the tracheobroncheal tree or esophagus. A perusal of contemporary literature will disclose the remarkable changes that it has wrought in our methods of diagnosis and therapy of these areas. The most important recent contribution has been the use of gastroscopy for visualization of the interior of the stomach.

Gastric Disease.—While gastroscopy has been an accepted adjunct in the removal of a foreign body from the stomach, its use in the inspection of the interior of that viscus has followed the recent development of the flexible gastroscope with a lens system by Schindler and Wolf. In a discussion of diagnostic gastroscopy by means of his instrument, Schindler¹ states that it is now possible to visualize the interior of the stomach with safety and with but little discomfort to the patient. It provides a means of direct morphologic diagnosis of gastric lesions. It can reveal the presence of a gastritis and hypertrophic gastritis. It is of definite aid in the differential diagnosis between ulcer and neoplasm, and also is of aid in observing the extent of the lesion as well as its progress or response to treatment. The contraindications to gastroscopy are the presence of esophageal disease, aneurysm of the aorta and dangerous cardiac conditions. Benedict,² in a preliminary report upon the use of this method in 75 patients, was impressed with the ease and harmlessness of gastroscopy. He feels that it is a valuable adjunct to the roentgenography in the study of gastric disorders especially in the investigation of gastritis and in the differentiation between ulceration and new growths. The danger in gastroscopy as the Jacksons³ point out

consists in the possibility of perforation of the esophagus during its introduction. They believe that the open tube is less dangerous, as the operator can always see a lumen ahead and stop the instrument if no lumen is visible. The Schindler instrument does not give a view of the lumen ahead and for that reason the operator must assure himself of the absence of esophageal disease by preliminary Roentgen examination or open tube esophagoscopy if necessary. They also point out that the removal of a foreign body or the performance of a biopsy require an open gastroscope rather than the Schindler instrument. They feel that every patient with gastric symptoms or hematemesis should have a diagnostic gastroscopy unless definite contraindications are present. This is especially true when a diagnosis of a gastric neurosis is contemplated in order that organic disease be excluded. Edwards⁴ states that gastroscopy is a valuable adjunct in the diagnosis of gastric disease but does not displace roentgenology. He believes that more experience is necessary in the interpretation of the findings, but feels that it is the best means at our disposal in establishing a diagnosis of chronic gastritis. Benedict⁵ feels that the diagnosis of chronic gastritis had rested upon an insecure foundation in the past. It was based mainly upon the presence of an indefinite symptomatology and the exclusion of organic gastric changes by means of the Roentgen ray. He emphasized that chronic gastritis is a definite disease most accurately diagnosed by gastroscopy. Jones, Benedict and Hampton⁶ observed 5 cases of pernicious anemia in which careful studies of the stomach were made including Roentgen ray, biopsy, direct observation at laparotomy and by gastroscopy. They found atrophy of the mucosa to be present mainly during a relapse but was not consistent. They noted the disappearance of the atrophy upon the employment of a specific therapy. Chevallier⁷ describes a non-inflammatory form of edema of the mucosa in the pyloric antrum of several cases of hypersensitivity that were studied with the gastroscope. The lesion appeared as a localized light rose-colored swelling, appearing and disappearing rapidly. It was associated with asthma, urticaria or other allergic states and was favorably influenced by desensitization. Jackson⁸ expressed the opinion that the day was not far distant when gastroscopy would be routinely employed in the study of patients presenting gastric symptomatology. He stressed the important contraindications in the use of the flexible gastroscope but insisted that the instrument marked a new era in the investigation of the stomach.

Neoplasms of the Tracheobronchial Tree.—Neoplasms of the trachea are quite rare. In fact, Simpson and Moore⁹ in their report of a case of primary adenocarcinoma located in the lower third of the trachea were able to find but 28 cases reported in the literature. They find that the occurrence of dyspnea in a person otherwise in good health and without evidence of intrathoracic disease is suggestive of tracheal new growth which can only be positively discovered by the aid of the bronchoscope. Guttman¹⁰ reports a case of cylindroma or adenocystic basal-cell carcinoma originating in the trachea bringing the reported number of primary tracheal malignancies to 29. The presenting symptom in this case also was dyspnea without other evidence of intrathoracic disease and was similarly discovered by diagnostic bronchoscopy. Richards and Dietrich¹¹ observed a child of 8 months with dyspnea and

wheezing which was due to a primary fibrosarcoma of the trachea that was found at postmortem. Jackson's old truism that "all that wheezes is not asthma" is applicable to tracheal neoplasms.

For some reason the popular belief obtains that benign neoplasms of the bronchi are uncommon. Morlock and Pinchin,¹² in a study of 150 cases of bronchial neoplasm, found 9 (6%) to be benign. These 9 cases were reported in detail. The authors stress the fact that such benign neoplasms should be diagnosed early and removed by bronchoscopy in order to obviate the permanent damage to the lung that may follow prolonged bronchial obstruction. Benign or "carcinoid" epithelial tumors are commonly found in the large bronchi. Kernan¹³ gives a detailed report of 10 cases. The bronchoscopic appearances were characteristic. The tumors were soft, at times moving with respiration. They bled readily upon being touched with the bronchoscope or biopsy forceps. Smaller growths could be removed with the biopsy forceps while larger growths necessitated the use of diathermy. Miller¹⁴ reported a similar case in which bronchoscopy was employed to discover the cause of an upper lobe atelectasis. It was found to be due to a soft tumor that histologically showed epithelial cells in glandular arrangement and many bloodvessels. The bronchoscopic removal of the neoplasm cleared the atelectasis. An adenomatous polyp of the right main bronchus was found to be the cause of an atelectasis by Rosenblum and Klein¹⁵ in a boy of 11, with improvement following the bronchoscopic removal. Kramer and Som,¹⁶ in a review of 23 cases of adenoma of the bronchi, emphasize the benign nature of these neoplasms. They commonly cause hemoptysis, cough, wheezing, and show Roentgen evidence of obstruction and its consequences, namely, atelectasis, and ultimately, chronic suppuration and bronchiectasis. In all cases bronchoscopic removal is to be attempted and failing that the use of irradiation is to be considered. They find that 17 of their 23 patients were alive after an average period of observation of 4 years.

In no field of medicine has greater progress been made than in the endoscopic study of malignant growths of the lung. Bronchoscopy can justly claim credit for the remarkable advances that have been established. In fact, prior to the use of endoscopic methods our knowledge of these neoplasms was restricted to what information we obtained from autopsy material in the dead house. Lloyd,¹⁷ in a study of 31 cases of bronchial malignancy, ranks bronchoscopy first in the methods of diagnosis, although 35% of his cases originated in the lung parenchyma which does not lend itself to endoscopic examination. He was able to obtain a satisfactory biopsy specimen in 17 of 24 cases in which bronchoscopy was performed. Moersch and Bowing¹⁸ report a case of adenocarcinoma of the bronchus and emphasize the importance of bronchoscopic study in all cases of vague and indefinite pulmonary symptomatology no matter what the Roentgen findings may be. For it is quite apparent that only endoscopy can discover early and small lesions of the bronchi.

Hemoptysis.—One of the most common symptoms of pulmonary malignancy is hemoptysis. As a rule, this is small in amount yet Lederer¹⁹ reports a case of fatal hemorrhage following bronchoscopy in a patient with an adenocarcinoma of the lung. Hemoptysis may be of other origin than carcinoma of the lung. Gerlinge²⁰ states that bron-

choscopy is indispensable in cases of hemoptysis of unknown origin, especially when there is no evidence of disease obtained by physical examination or Roentgen ray. He found bleeding may be due to dilated vessels or small neoplasms or other lesions that are insufficient to cause signs of its presence by effecting physical findings or noticeable Roentgen ray phenomena. Many cases of tracheal syphilis, tuberculosis, carcinoma, papilloma, angioma, varix and ulcer may cause hemoptysis without evidencing any physical or Roentgen ray findings. Mounier-Kuhn²¹ describes a case of hemoptysis due to hemorrhagic tracheitis. The tracheal mucosa in this instance was found to be deeply injected, thickened and hyperemic, with obliteration of normal tracheal landmarks.

Pulmonary Atelectasis.—Pulmonary atelectasis as a consequence of surgery, foreign body in the lung, and bronchial neoplasm is quite well recognized. However, that atelectasis may follow a tuberculous hemoptysis is not so well known. Heaton²² reported a case in which dyspnea, physical and Roentgen findings indicated a blockage of the bronchus and atelectasis of the lower right lobe. At bronchoscopy, many blood clots, found as bronchial casts, were removed from the right bronchus with subsequent reëxpansion of the lung and relief of dyspnea. There was a recurrence of the incident some 6 weeks later with similar relief afforded by bronchoscopic removal of the clots. Chronic empyema may be caused by an unrelieved postpneumatic atelectasis with empyema, is the belief of Butler.²³ He feels that atelectasis may cause fibrosis of the lung parenchyma and chronic empyema that can only be relieved by extensive thoracoplasty. He states that atelectasis should be suspected when postpneumonic empyema fails to clear within a reasonable time and favors bronchoscopy for diagnosis and endobronchial aspiration. He reports a case in which bronchoscopy caused improvement in breathing and ultimate cure in postpneumonic empyema when palliative measures failed.

Pulmonary Suppuration.—Aspiration has always been conceded to be an important etiologic factor in pulmonary suppuration. Lowenthal²⁴ investigated 21 patients who had been operated upon in other fields than the upper respiratory or food passages, under general anesthesia. Immediate bronchoscopy following the termination of the operation disclosed pharyngeal secretions in the tracheobronchial tree in 76% of the patients; thus concurring in views held by many that aspiration is a most important factor in the production of postoperative pulmonary infections. He advocated frequent suction to the pharynx during anesthesia to decrease the amount of secretion available for aspiration.

Bronchoscopic therapy of lung suppuration continues to be the subject of many contributions to the literature. Looper²⁵ advocates endoscopic treatment of central abscesses especially if they communicate with a bronchus. He also favors endoscopy in cases of multiple lung abscess in which surgery is contraindicated. Rist and Soulas²⁶ stressed that the most brilliant results of endoscopic treatment of abscess were in those cases in which treatments were instituted early, *i. e.*, within the first 3 or 4 weeks after the formation of the abscess. They found that decided clinical improvement could be depended upon after 4 to 6 bronchoscopic treatments and that all but one of their patients required no more than 9. They feel that if prompt improvement is

not noted surgical intervention is to be considered. In another contribution, Soulas²⁷ concludes that endoscopic therapy is more successful in acute abscess than in chronic, curing 50% of the acute cases as compared to 15% of the chronic cases subjected to endoscopic therapy. Kernan²⁸ also stresses the importance of endoscopic treatment in early lung abscess and confesses its ineffectiveness in bronchiectasis. Pinchin and Morlock²⁹ are convinced that the early use of the bronchoscope aids in the resolution of the first stages of abscess formation in the period of pneumonitis. He feels that endoscopy is harmless and for that reason waiting to determine if an incipient infection will undergo spontaneous resorption is to risk the formation of an abscess that might necessitate longer treatment and possible surgery. Moore and Love³⁰ presented a preliminary report of their experience with the bronchoscopic application of an active polyvalent staphylococcic bacteriophage in 28 patients, 14 of whom had bronchiectasis, 10 pulmonary abscess, and 3 chronic bronchitis. By means of the bronchoscope they instilled 5 cc. of the bacteriophage into the affected bronchus that had been previously freed of secretions and any mechanical obstructions. Of 10 patients treated with a commercially obtained phage 4 showed improvement; of 18 treated with their own specially prepared phage, 17 showed improvement after but two instillations.

Dyspnea.—Barach³¹ has introduced a noteworthy therapeutic agent in the treatment of dyspnea due to asthma and obstructive tracheo-bronchial lesions. He advocated the use of helium in a helium oxygen mixture to take the place of the conventional nitrogen-oxygen mixture. The lower specific gravity of the helium as compared to the nitrogen would give a mixture much less dense than that of air and would consequently be easier to breathe. This mixture was of marked benefit in 4 cases of asthma in which it was used. Two infants with obstructive lesions in the larynx and trachea were similarly benefited. This may prove to be a most valuable addition to our therapeutic armamentarium.

Esophageal Disease. Dysphagia.—The investigation by McGibbon³² of 7 patients afflicted with dysphagia associated with anemia, reported in the literature as the Plummer-Vincent Syndrome, revealed the presence of organic esophageal lesions in 6. These were spasm and membrane at the esophageal introitus, stricture or web at the cricoid area, and chronic esophagitis. It is possible that the anemia is consequent to the restricted dietary due to the dysphagia.

Dysphagia due to esophageal stenosis following the ingestion of lye is well known. Other substances may cause similar catastrophe. Pitkin³³ reported a case of stricture due to the accidental administration of lactic acid. The infant was being fed a milk mixture acidified by the addition of lactic acid and was given the acid by mistaking the identity of the bottle. Dysphagia, due to stricture, appeared some 3 weeks later and required gastrostomy and retrograde dilatation. Kearney³⁴ reports a similar case due to the ingestion of sulphuric acid. It is obvious that more care should be exhibited in the handling of such escharotic agents. Careful labeling and identifying bottle structure should be enforced by law for all mixtures containing caustic preparations, such as paint removers, drain-pipe cleaners and the like, that are used universally today. That such legislation is effectual is proved by a survey of esophageal stricture resulting from caustic alkalies made by

Taylor.³⁵ He found a decrease of more than 50% in the incidence in states in which legislation has gone into effect, in spite of the enormous increase in the use of such chemicals. Dysphagia may also be due to a paraesophageal diaphragmatic hernia. Vinson and Moersch³⁶ report several cases associated with intermittent dysphagia and pain. They were able to discover by esophagoscopy the presence of a stricture in 2 cases and cardiospasm in a third.

Neoplasms.—While most neoplasms of the esophagus are malignant, occasionally benign growths are encountered. Such growths are usually difficult to discover and may be only found by esophagoscopy. Moersch and Broders³⁷ report a case of adenoma of the esophagus that caused dysphagia and epigastric burning. Roentgenologic study revealed an unusual narrowing of the esophagus which at esophagoscopy showed as a flat mass. A piece taken for biopsy was ultimately reported as an adenoma. In addition the patient was found to have a duodenal ulcer.

Carcinoma of the esophagus is well known as a clinical entity. It is unfortunate, however, that the usual picture of the disease that we are accustomed to recognize is the terminal one and therefore is of little value in aiding the patient. Our efforts must be extended in attempting to recognize the early stages of the growth. Jackson³⁸ believes that this lamentable inability to make an early diagnosis is in a great measure responsible for the practically 100% mortality associated with carcinoma of the esophagus. Roentgen study and esophagoscopy are, therefore, indicated in every case of disturbance of the swallowing function. Not all carcinomas of the esophagus give rise to dysphagia. Mathews and Schnabel,³⁹ in a clinical and pathologic study of 108 autopsies, find that some 20% of esophageal carcinomas are non-stenosing and therefore not apt to cause dysphagia. These non-stenosing growths were usually found in the lower two-thirds of the viscus. The treatment of this disorder, as a rule, is a fruitless one, although Steele⁴⁰ believes the use of endoscopic introduction of radon seeds associated with deep external irradiation may have certain possibilities.

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PHYSIOLOGY

PROCEEDINGS OF THE PHYSIOLOGICAL SOCIETY OF PHILADELPHIA SESSION OF OCTOBER, 19, 1936

A New Graphic-Mathematical Analysis of Absorption Spectra, as Applied to Hemoglobin Derivatives.—D. L. DRABKIN (Department of Physiological Chemistry, University of Pennsylvania). The absorption spectra in the visible and ultraviolet regions (from $\lambda 700$ to $\lambda 200 \text{ m}\mu$) of various hemoglobin derivatives—oxyhemoglobin, carboxyhemoglobin, acid and alkaline methemoglobins, cyanmethemoglobin and pyridine hemochromogen—have been subjected to analysis.

The positions of most of the maxima in the absorption curves of these hemoglobin derivatives are at equal frequency distances from each other. These positions may be expressed by $n = \frac{\nu \times 10^{-2}}{\nu_0 \times 10^{-2}}$, where n is an integer (4, 5, 6, 7, 8, 9, 10 and 11 in the spectra studied) and $\nu_0 \times 10^{-2}$, representing the fundamental frequency, is 40. Two other maxima in the green region (visible), which do not belong to the above series, are also present in all the derivatives.

The graphic-mathematical analysis indicates that the absorption curves are the additive result of individual units or bands, which may be conveniently expressed as normal frequency curves of the form $y = kc - \frac{(x - a)^2}{2\sigma^2}$. The summation, Σ , of unit curves of this type

accurately reproduces the total absorption curve, which is mathematically given by $\Sigma y = kx - \frac{(x - [n.40])^2}{2\sigma^2}$

The analysis brings out the non-obvious, fundamental similarity in the absorption spectra of the various hemoglobin derivatives, and may lead to an understanding of certain problems in connection with the molecular structure of these substances.

Enlarged Hypophyses in Old Albino Rats.—W. H. F. ADDISON (Department of Anatomy, University of Pennsylvania). Greatly enlarged hypophyses have been found infrequently in old rats of both sexes in The Wistar Institute colony. The weight of the enlarged hypophyses averaged 20 times that found in other animals of the same age. Thus in a female of 1028 days, the enlarged hypophysis weighed 0.238 gm., and in a female of 961 days with an hypophysis of the usual size, the weight of the hypophysis was 0.0116 gm. In a male of 960 days, the weight of the enlarged hypophysis was 0.279 gm. and in a male of 1100 days, the weight was 0.012 gm. All the rats were of normal body size. The other ductless glands were weighed, but the weights showed nothing significant. Microscopic sections of the enlarged hypophyses show, in the pars anterior propria, the presence of numerous thin-walled blood channels, many widely distended with blood and some hemorrhagic areas. There is great increase in the gland-cell population and the cells are nearly all of the chromophobe undifferentiated type.

The Effect of Pituitrin, Water, Theophylline and Salyrgan on the Renal Blood Flow and Creatinine Clearance of Unanesthetized Rabbits and Dogs.—A. M. WALKER, C. F. SCHMIDT, K. A. ELSOM, and C. G. JOHNSTON (Laboratories of Pharmacology and Research Surgery, University of Pennsylvania). Renal blood flow was measured by an electrical thermostromuhr recently described by Schmidt and Walker; at the end of each experiment the instrument, undisturbed in its position on the renal artery, was calibrated by comparison with the method of Barcroft and Brodie. Creatinine clearances were measured by the usual technique.

Antidiuresis was produced in 20 animals by the subcutaneous injection of pituitrin. The renal blood flow and creatinine clearances remained substantially unaltered. Clearly, renal vasoconstriction was not responsible for the antidiuresis.

Water, administered by mouth to 36 animals, produced tenfold increases in urine volume. There was no consistent increase in renal blood flow as the diuresis developed and in 123 of 211 periods where urine volume changed the renal blood flow did not alter in the same direction. Creatinine clearances in dogs showed no consistent change; in rabbits they usually increased but not to a degree proportional to the diureses.

Renal blood flow was increased during the diureses produced by theophylline in 11 rabbits but the increase endured only one-third as long as the diuresis. Although the creatinine clearances usually rose, the increases were not proportional to the extent of the diureses.

During diureses produced by salyrgan in 10 dogs, the renal blood

flow showed no increase above the control level in 7 instances. The creatinine clearances were usually decreased.

It is concluded that, insofar as renal blood flow and creatinine clearances reveal glomerular function, the glomerulus plays a very subsidiary rôle in regulating urine volume. The average renal blood flow in unanesthetized rabbits was found to be 3.2 cc. per gram per minute, the average percentage of plasma filtered by the glomeruli to be 30.2.

The Relative Biological Effectiveness of Fast Neutrons and Roentgen Rays Upon Different Organisms.—R. E. ZIRKLE (Johnson Foundation, University of Pennsylvania, with collaboration of P. C. AEBERSOLD and E. R. DEMPSTER, University of California). Large numbers of two small organisms—the *Drosophila* egg and the wheat seedling—were irradiated with various amounts of 200 kv. Roentgen rays and of fast neutrons generated in the University of California cyclotron.

For the wheat seedling, one ionization unit of neutrons was found to be biologically equivalent to 5 units of Roentgen rays, whereas for the *Drosophila* egg 1 unit of neutrons was equivalent to only 2 units of Roentgen rays. Hence, in general, the biologic effectiveness of neutrons relative to Roentgen rays is greater for some cells than for others. This general fact has important practical implications, for it indicates the possibility that the effectiveness of neutrons upon tumors *in vivo*, relative to Roentgen rays, may be greater than upon normal tissues.

Correction. On page 705 of the last number (November) of this JOURNAL the Editor inserted a footnote based on erroneous information which he now wishes to correct with apology to the makers of orthoiodoxybenzoate. It is not correct that this drug contains cincophen, also the agranulocytosis patient referred to was later found to have taken fairly large doses of a drug containing amidopyrine as well.—EDITOR.

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